

ANNALS OF INTERNAL MEDICINE

VOLUME 34

JANUARY, 1951

NUMBER 1

TREATMENT OF TYPHOID FEVER. I. COMBINED THERAPY WITH CORTISONE AND CHLORAMPHENICOL *

By JOSEPH E. SMADEL, *Washington, D. C.*, HERBERT L. LEY, JR., *Boston, Massachusetts*, and FRED H. DIERCKS, *Washington, D. C.*

CHLORAMPHENICOL now has an established place in the treatment of typhoid fever.^{1, 2, 3, 4, 5} However, it has been our observation, as well as that of others, that little if any clinical improvement occurs during the first 36 hours of therapy and that the patients do not become afebrile until about the fourth day. This delay in therapeutic response is difficult to explain, since previous experience shows that the bacterial organisms are promptly controlled by specific therapy.³ Indeed, the bacteremia ceases several days before fever and toxemia subside. However, it has seemed reasonable to postulate that the delayed clinical response of typhoid patients to chloramphenicol is dependent upon a reaction of the host to the products of bacterial and tissue destruction which existed at the time of institution of therapy.

Recent experience in a number of institutions suggests that the presence of increased amounts of adrenal cortical hormones has an effect, sometimes beneficial, on the clinical course of several infectious diseases.^{6, 7, 8, 9, 10} We considered the possibility that the toxemia of typhoid fever might be affected by appropriate doses of cortisone acetate (Cortone †). Accordingly, a group of patients with typhoid fever was given cortisone along with chloramphenicol. The results of this combined therapy are reported at this time.

MATERIALS AND METHODS

Selection of Patients: Using criteria and methods previously employed,^{3, 5} patients with typhoid fever, proved by cultivation of *Salmonella typhosa* from the blood or feces, were selected and treatment was begun between the

* Received for publication September 27, 1950.

From the Department of Virus and Rickettsial Diseases, Army Medical Department Research and Graduate School, and the Commission on Immunization, Armed Forces Epidemiological Board, Washington, D. C.

† Trade name of Merck and Company, Inc.

eighth and sixteenth day after onset of disease. All of the eight patients in the present study were hospitalized in or near Kuala Lumpur, Federation of Malaya: six at the General Hospital, and one each at Bungsar Hospital and British Military Hospital, Kinrara.

Treatment: Chloramphenicol,* supplied by Parke, Davis and Company, was given to adult patients on the following schedule: An initial oral dose of 3.0 gm. was followed by 1.5 gm. at 12 hour intervals on nine occasions, after which 1.5 gm. amounts were administered once daily for the next 10 or 11 days. Thus, the adults received approximately 50 mg. per kilogram of body weight as a loading dose and also daily during the initial four day period. During the extended latter portion of the regimen, the medication consisted of about 25 mg. per kilogram per day. The group included one child of 11 and one adolescent of 15 (N-18 and N-9) who received proportionate amounts of drug equivalent to the adult dose on the basis of body weight.

Cortisone was administered according to one of two schedules. The first group of patients received 200 mg. during the first 24 hours, followed by 100 mg. on each of the three succeeding days. The second group was given 300 mg. the first day, 200 mg. the second, and 100 mg. on each of the two succeeding days. The hormone preparation was injected intramuscularly at intervals of six to 12 hours, the amounts and times being adjusted to the daily requirement.

Care of Patients: Clinical and laboratory procedures were essentially the same as those employed in earlier studies by our group in Malaya.^{3, 5} Fever is defined in this report as any oral temperature above 99.0° F. Frequent chloramphenicol blood levels were determined in a few of the patients. The results were similar to those previously obtained with a regimen essentially identical⁵ with that currently used. Specimens of blood, feces and urine were cultured for *S. typhosa* at frequent intervals throughout the period of observation. In accordance with public health regulations in Malaya, prior to discharge from the hospital each patient provided three successive specimens of feces and urine, collected at weekly intervals, which failed to yield *S. typhosa* on culture.

RESULTS

Effect of Combined Chloramphenicol-Cortisone Treatment: Each of the eight patients in the current study was treated with chloramphenicol and cortisone. It has not been feasible for our present group to collect information at this time on the individual effect of each therapeutic agent. Therefore, we shall draw on our earlier experience with the use of chloramphenicol in typhoid fever and shall refer to the work of Woodward and his associates¹¹ for data on the effect of cortisone alone in patients with this disease.

Our previous experience with the use of chloramphenicol in the treatment of 44 patients with typhoid fever showed that an average of four days was required from the time the first dose of antibiotic was given until fever and

* Trade name, Chloromycetin.

toxemia disappeared.^{3, 5} In these 44 patients, the febrile illness lasted for a single day in one instance and for 11 days in another, but 36 of the 44 patients experienced three to five days of fever. Indeed, in the entire group only five had pyrexia of less than three days' duration, and in three fever persisted for six or more days. Thus, the four day interval of toxemia and fever is a fairly constant finding in typhoid patients who receive only chloramphenicol. Therefore, a new therapeutic regimen resulting in an appreciable and consistent reduction of the four day period presumably improves upon the original regimen with chloramphenicol alone.

Data on eight cases of typhoid fever that were treated with chloramphenicol in the usual manner but, in addition, received cortisone during the first few days of antibiotic therapy are summarized in table 1. The patients have been divided into two groups: group 1 received 2.8 to 3.6 (average of

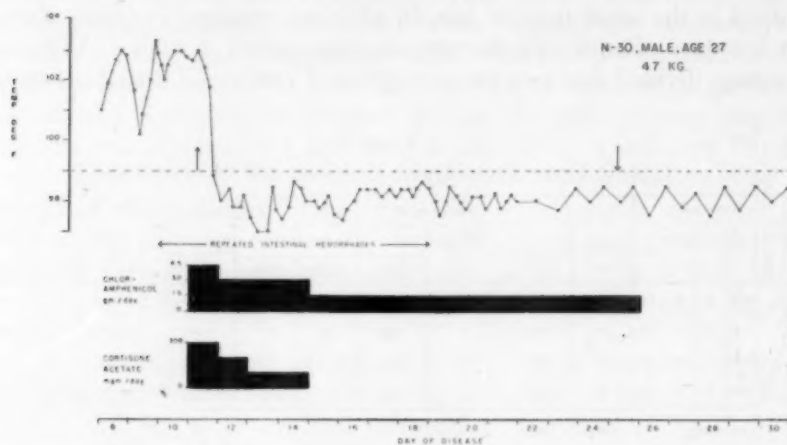
TABLE I
Typhoid Fever Treated with Cortisone and Chloramphenicol

PATIENT					TREATMENT					RESPONSE AFTER TREATMENT				TYPHOID LAST DAY POSITIVE
GROUP	NO.	AGE	SEX	WT. KG.	DAY OF DISEASE BEGIN	CORTISONE			CHLORAMPHENICOL		DURATION OF FEVER AFTER 5, HOURS	COMPLICATIONS		BLOOD STOOL
						MG./KG. FIRST 24 HR.	DAYS CONTINUED	TOTAL DRUG (MG.)	DAYS CONTINUED	TOTAL DRUG (MG.)		NATURE	ONSET, DAY OF DISEASE	
1	N-9	15	M	34	16	2.9	3	200	14	20	83	NONE		13 0
	N-12	18	F	55	15	3.6	4	500	14	27	61	RELAPSE	36	15 33
	N-18	11	M	36	12	2.8	4	250	14	20	18	NONE		9 16
	N-28	17	F	55	15	3.6	4	500	14	29	62	RELAPSE	43	44 36
	AVERAGE				14.5	3.2					50.2			
2	N-30	27	M	47	11	6.4	4	700	15	30	15	INTESTINAL HEMORRHAGE	10	11 9
	N-48	18	M	57	10	5.3	4	700	15	30	13	NONE		10 7
	N-50	38	M	54	13	5.6	4	700	18	47	11	NONE		9 14
	N-54	19	M	55	8	5.1	4	700	15	30	23	TACHYCARDIA	25	4 9
	AVERAGE				10.5	5.6					15.5			

3.2) mg. of cortisone per kilogram of body weight during the first 24 hours of therapy, while group 2 received 5.1 to 6.5 (average of 5.6) mg. per kilogram during the comparable period. While the results in both groups showed a consistent improvement over the earlier findings in patients treated solely with chloramphenicol, it is the response of the second group that received the larger dose of cortisone which deserves particular attention. It is to be noted that the four patients given 300 mg. of cortisone and 4.5 gm. of chloramphenicol during the first 24 hours were afebrile before the end of this period. In fact, patient N-50 had a normal temperature 11 hours after this regimen was instituted, and patient N-54, who had the most protracted course, became afebrile by the twenty-third hour.

Combined treatment was begun in each instance at 9:00 a.m., but little objective or subjective improvement was noted until the early evening. At

this time the patients, who had been in the semistuporous state which characterizes this stage of typhoid fever, displayed interest in their surroundings and their temperatures began to fall. By the next morning, i.e., at 24 hours, the findings in the group receiving the larger dose of cortisone were startling. They were all afebrile. Furthermore, three of the four were sitting up in bed and were so bright and cheerful that they seemed almost euphoric; moreover, they complained of hunger. The fourth member of the group, N-30, was alert and afebrile but weak as the result of previous intestinal hemorrhages. From this point onward, improvement in all patients was steady.



WBC x 1000	8.7	5.0	7.1	6.3	4.1	5.2	6.9	7.8	5.2
HGB GMS	15.7	15.7	10.8	10.5	9.0	7.9	8.5	8.8	8.8
STYPHOSE CULTURE	BLOOD	+	+	+	0	0	0	0	
	STOOL	+	0	0	0			0	0
	URINE							0	0

FIG. 1. Patient with typhoid fever who received combined therapy with the larger dose of cortisone and the usual amount of chloramphenicol. The patient became afebrile in 15 hours.

The response in those persons who received the smaller dose of cortisone, group 1, was not so dramatic as that of the group discussed above. The average duration of fever in group 1 was 50.2 hours and in group 2, 15.5 hours (see table 1). No troublesome side effects attributable to cortisone or to the combined therapy were noted.

The record of N-30, which is presented graphically in figure 1, illustrates the response of a typhoid patient to combined therapy with the larger dose of cortisone and the usual amount of chloramphenicol. A summary of the clinical course follows:

Patient N-30. This 27 year old Malay male was admitted to the General Hospital on the eighth day of an illness characterized by chills, high fever and a nonpro-

ductive cough. *S. typhosa* was cultured from specimens of blood and feces obtained prior to initiation of therapy on the eleventh day of illness (see figure 1). Within 15 hours of the beginning of the treatment, at a time when he had received a total of 200 mg. of cortisone and 4.5 gm. of chloramphenicol, the patient became afebrile and alert. His illness was complicated by a series of severe intestinal hemorrhages which began on the tenth day, prior to treatment, and continued until the eighteenth day after onset. During this time the hemoglobin dropped from 15.7 to 7.9 gm. per cent. In spite of the continuing blood loss and the resulting anemia his general condition improved steadily, but his status remained uncertain until the intestinal bleeding stopped. Parenteral fluids, including whole blood, were reserved for use in case of shock, which did not develop.

Repeated attempts to culture *S. typhosa* from specimens of feces and blood taken after the ninth and eleventh days, respectively, yielded negative results. The patient was discharged from the hospital on the fifty-fourth day after onset. When re-examined on the seventy-sixth day his general condition was excellent; his anemia had responded well to supplemental iron therapy, and cultures from his feces failed to yield *S. typhosa*.

Complications: The common complications of typhoid fever are intestinal hemorrhage, intestinal perforation, and relapse; the incidence of these in the days before specific therapy was approximately 7, 3 and 9 per cent, respectively.¹² None of the present group of patients had perforation and only one had severe hemorrhage. The occurrence of two relapses was unexpected among eight patients who received combined therapy which included chloramphenicol for a period of 14 or 15 days. Previous experience had indicated that a high relapse rate results when chloramphenicol was administered for eight days or less, but that few relapses were encountered when therapy was continued for two to three weeks.⁵

The relapses of typhoid fever in patients N-12 and N-28 differed in no way from those previously observed in Malayan patients following inadequate chloramphenicol therapy. They responded satisfactorily when the antibiotic was again administered. It is worth noting that during these episodes cortisone therapy was not repeated, and that the interval between beginning treatment with chloramphenicol and the disappearance of fever was 72 and 69 hours.

Figure 2 presents graphically the findings in patient N-12 who suffered a relapse. A brief description of her course follows:

Patient N-12. This 18 year old Chinese female was admitted to the General Hospital on the thirteenth day of an illness characterized by fever, diarrhea and headache. *S. typhosa* was cultured from specimens of blood and feces obtained on the fifteenth day of disease immediately prior to initiation of therapy (see figure 2). The response of this patient who received the lower dose of cortisone was less rapid than that observed in members of group 2, who were given the larger dose. Her fever continued for 36 hours and then dropped promptly to a normal level. About this time she became alert and almost euphoric. She had then received 300 mg. of cortisone and 7.5 gm. of chloramphenicol. Because of the low-grade fever on the seventeenth day, a total of some 60 hours elapsed before she remained afebrile. The patient improved steadily and appeared to be making an uneventful recovery when a relapse of typhoid fever began on the thirty-sixth day after onset. Chloramphenicol without cortisone

was used to terminate this episode, but it was 72 hours before the patient became permanently afebrile. Henceforth, convalescence was uneventful and the patient was discharged from the hospital on the seventieth day.

S. typhosa was not demonstrated in the blood or feces of the patient on the day following initial treatment nor subsequently until the thirty-second day after onset. At this time, four days after the last dose of chloramphenicol and five before the clinical relapse, the organisms were again found in the feces and were still present 24 hours later. Repeated attempts to cultivate *S. typhosa* from the blood and feces immediately prior to, during and for four weeks following the relapse gave negative results.

Patient N-54 developed an unexplained tachycardia on the twenty-fifth day of disease, which was three days after treatment had been completed and 16 days after his last elevation of temperature. At this time the pulse rate in-

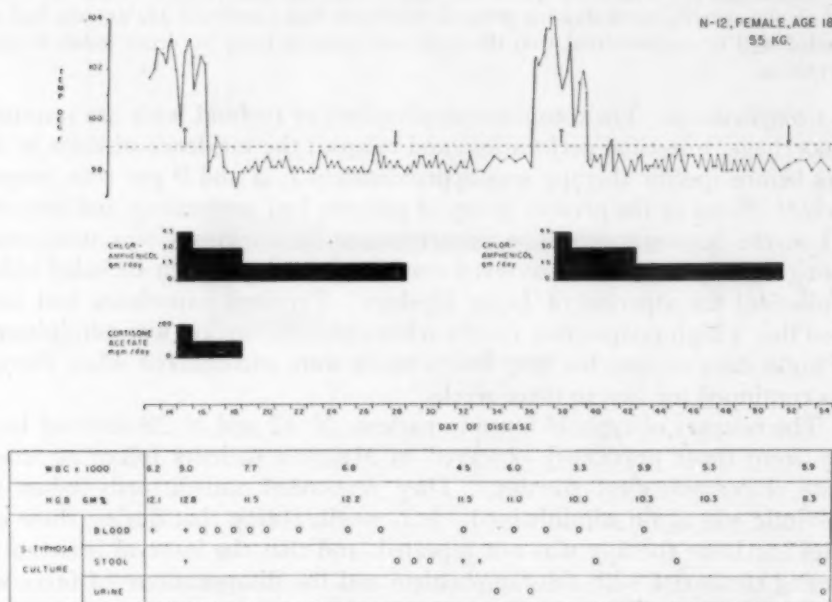


FIG. 2. Typhoid patient who suffered a relapse following combined therapy with cortisone and chloramphenicol.

creased to a regular rhythm of 120 to 130 beats per minute, whereas during the preceding two weeks it had remained between 80 and 90. Electrocardiographic facilities were not available, but clinical tests tended to rule out auricular flutter as a cause of the increased rate. The tachycardia persisted at this level for several days and then gradually returned to normal.

Laboratory Studies: The results of the usual laboratory tests, other than those connected with cultivation of *S. typhosa*, added nothing to the general knowledge.

S. typhosa was not recovered from the blood of patients 24 hours after therapy was begun or subsequently, except from patient N-28, who had bac-

teremia during her relapse. Feces from patients N-50 and N-54 obtained 24 hours after instituting therapy contained *S. typhosa*, while patient N-18 provided a positive specimen as late as the fourth day (see table 1). All other fecal specimens cultured after therapy gave negative results, except for several from patients N-12 and N-28, who again shed the organism a few days prior to their clinical relapses. None of the urine specimens contained demonstrable *S. typhosa* before, during or after treatment.

DISCUSSION

There appears little doubt that the simultaneous administration of cortisone and chloramphenicol terminates the acute manifestations of typhoid fever more promptly than does chloramphenicol alone. It is assumed that this is desirable. On the other hand, we are not convinced that the feeling of well being, bordering on euphoria, which was noted in our patients 24 hours after combined therapy was begun provides a sound criterion for estimating the adequacy of control of the disease. As was pointed out before,^{3,5} the lesions of typhoid fever require time for repair even after the bacterial multiplication has been suppressed by chloramphenicol. Therefore, one cannot expect that the hazards of intestinal perforation and hemorrhage will disappear as promptly as the fever. Although the period of bleeding in patient N-30 was not unduly prolonged, the possibility that cortisone therapy may have delayed healing must be considered and evaluated in other studies.

The occurrence of two relapses of typhoid in the present group of eight cases provided a higher incidence than would ordinarily be expected in patients who received a full two weeks course of chloramphenicol.⁵ Whether this was mere coincidence or was related to the supplementary use of cortisone cannot be stated at this time. The second possibility should be borne in mind, however, until the results of future investigations provide definitive information on this point. The serologic response of the present patients, as exemplified by the Widal reaction, was not investigated, since the results of this agglutination test were not employed in establishing the diagnosis of typhoid fever, and since the titers in recovered patients are so variable that no valid conclusions could be drawn from the data on the present small group. It may be noted, however, that Mirick¹³ has demonstrated that patients who were receiving cortisone or ACTH for one or another disease retained a normal capacity to produce antibodies following vaccination with pneumococcal polysaccharides.

The maximal benefit attributable to cortisone was obtained in those patients who received the larger dose of hormone, i.e., a total of 300 mg. during the first day, or 5 to 6 mg. per kilogram of body weight during this period. The patients in this group became afebrile in 15.5 hours on the average. Cortisone was not administered beyond the third or fourth day because the chloramphenicol regimen of itself would usually have terminated the acute episode by this time. It is problematical whether cortisone need be continued

after the temperature has returned to normal. We suspect that a total course of 300 mg. given during the first day would have elicited the maximal effect and that chloramphenicol by itself would have been sufficient thereafter.

At the present stage of our knowledge regarding the mode of action of cortisone, one can only speculate on how it helps in the treatment of typhoid fever. Before beginning these studies, we were of the opinion that the toxic manifestations, which continued unabated for several days after the growth of *S. typhosa* apparently had been controlled by chloramphenicol, were dependent upon the liberation of toxin from the pathogenic bacteria already present and on the absorption of noxious products from the extensive necrotic process in the lymphoid system of the host. The observations of Lewis and Page¹⁴ indicated that adrenalectomized rats were more resistant to the shocking action of typhoid toxin if they were treated with cortisone. Our own observations subsequently showed that mice with intact adrenal glands when injected with ACTH or cortisone were as susceptible as control animals to the toxins of rickettsiae and of *S. typhosa*.¹⁵ These observations are not contradictory, but instead suggest that the protective effect of cortisone noted by Lewis and Page is the result of the action of the hormone on the abnormal host and not on the toxin itself. Consequently, we prefer to consider the beneficial effect of cortisone in the typhoid patient as resulting from action on the human host rather than directly on the typhoid organism or its products.

Woodward and his associates¹¹ have made particularly interesting observations on a number of typhoid patients who were treated with cortisone alone. These patients became afebrile and atoxic about as rapidly as did those in the present study who received combined therapy, even though *S. typhosa* was apparently not controlled by the cortisone. The use of cortisone alone in the treatment of typhoid fever is not recommended as a general therapeutic measure. On the other hand, its combination with chloramphenicol may be desirable in selected cases.

SUMMARY

Combined therapy with cortisone and chloramphenicol provides more prompt relief from the clinical manifestations of typhoid fever than does treatment with chloramphenicol alone. Earlier experience demonstrated that about four days were required on the chloramphenicol regimen before fever and toxemia disappeared. Typhoid patients who received 200 mg. of cortisone the first day and 100 mg. thereafter for several days in addition to chloramphenicol had an average febrile period of 50.2 hours. Those who received 300 mg. of cortisone the first day, followed by decreasing amounts along with chloramphenicol, were febrile for an average of 15.5 hours.

The combined therapy appears to be of sufficient theoretic and practical interest to warrant further study.

ACKNOWLEDGMENT

The authors wish to thank Dr. J. W. Field, Director of the Institute for Medical Research, and the staff of the Institute for their assistance in this work. Grateful acknowledgment is also made of the coöperation of the directors and the untiring assistance of the medical and nursing staff members of the General Hospital, Bungsar Hospital, and British Military Hospital, Kinrara, Kuala Lumpur.

BIBLIOGRAPHY

1. Woodward, T. E., Smadel, J. E., Ley, H. L., Jr., Green, R., and Mankikar, D. S.: Preliminary report on the beneficial effect of chloromycetin in the treatment of typhoid fever, *Ann. Int. Med.* **29**: 131-134, 1948.
2. Smadel, J. E.: Chloramphenicol (chloromycetin) in the treatment of infectious diseases, *Am. J. Med.* **7**: 671-685, 1949.
3. Woodward, T. E., Smadel, J. E., and Ley, H. L., Jr.: Chloramphenicol and other antibiotics in the treatment of typhoid fever and typhoid carriers, *J. Clin. Investigation* **29**: 87-99, 1950.
4. Anonymous: Chloromycetin in typhoid fever, *Lancet* **1**: 720-722, 1950.
5. Smadel, J. E., Bailey, C. A., and Lewthwaite, R.: Synthetic and fermentation type chloramphenicol (chloromycetin) in typhoid fever: prevention of relapses by adequate treatment, *Ann. Int. Med.* **33**: 1-17, 1950.
6. Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: compound E) and of pituitary adrenocorticotrophic hormone on rheumatoid arthritis; preliminary report, *Proc. Staff Meet., Mayo Clin.* **24**: 181-197, 1949.
7. Bowland, E. W., and Headley, N. E.: Effects of cortisone acetate on rheumatoid arthritis, *J.A.M.A.* **141**: 301-308, 1949.
8. Elkinton, J. R., Hunt, A. D., Jr., Godfrey, L., McCrory, W. W., Rogerson, A. G., and Stokes, J., Jr.: Effects of pituitary adrenocorticotrophic hormone (ACTH) therapy, *J.A.M.A.* **141**: 1273-1279, 1949.
9. Coriell, L. L., Siegel, A. C., Cook, C. D., Murphy, L., and Stokes, J., Jr.: Use of pituitary adrenocorticotrophic hormone (ACTH) in poliomyelitis, *J.A.M.A.* **142**: 1279-1281, 1950.
10. Finland, M., Koss, E. H., and Ingbar, S. H.: Effects of ACTH in primary atypical (viral) pneumonia and in pneumococcal pneumonia (preliminary report), Chapter 45 in: Mote, J. R.: *Proceedings of the first clinical ACTH conference, 1950*, Blakiston, Philadelphia, p. 529.
11. Woodward, T. E., Hall, H. E., Dias-Rivera, R., Hightower, J. A., Martinez, E., and Parker, R. T.: Treatment of typhoid fever. II. Control of clinical manifestations with cortisone, *Ann. Int. Med.* **34**: 10-19, 1951.
12. McCrae, T.: The symptoms of typhoid fever, Chapter IV in: Osler, W., and McCrae, T.: *Modern medicine, Volume II, Infectious diseases, 1907*, Lea Brothers and Company, Philadelphia, p. 104.
13. Mirick, G. S.: The effect of adrenocorticotrophic hormone and cortisone on antibody production in human beings, *J. Clin. Investigation* **29**: 836, 1950 (abstract).
14. Lewis, L. A., and Page, I. H.: Studies on the protective power of adrenal extract and steroids against bacterial toxins in adrenalectomized rats, *Appendix 1 to: Kendall, E. C.: The chemistry and partial synthesis of adrenal steroids, Ann. New York Acad. Sc.* **50**: 547-551, 1949.
15. Jackson, E. B., and Smadel, J. E.: Cortisone and ACTH on toxins of rickettsiae and *Salmonella typhosa*, *Bact. Proc.* 92-93, 1950 (abstract).

TREATMENT OF TYPHOID FEVER. II. CONTROL OF CLINICAL MANIFESTATIONS WITH CORTISONE *

By T. E. WOODWARD, M.D., *Baltimore, Maryland*, H. E. HALL, M.D., R. DIAS-RIVERA, M.D., J. A. HIGHTOWER, M.D., E. MARTINEZ, M.D.,
San Juan, Puerto Rico, and R. T. PARKER, M.D.,
Baltimore, Maryland

DESPITE the obvious benefits of chloramphenicol therapy in typhoid fever,^{1,2} there are several problems in this disease which remain to be solved: (1) The present chloramphenicol regimens do not alleviate the toxemia of the disease for at least 36 to 48 hours and fail to eliminate the fever until about the fourth day; (2) relapses of typhoid fever occur in a certain percentage of treated patients³; (3) *Salmonella typhosa* continues to be shed in the feces for variable periods of time after therapy is begun,² and (4) the typhoid carrier state when it exists is not permanently benefited by chloramphenicol.²

The protective effect of cortisone against the shocking action of typhoid toxin in adrenalectomized rats was clearly demonstrated by Lewis and Page.⁴ In similar experiments conducted with normal mice by Smadel and Jackson⁵ no protection was noted. The results of these two groups of investigations suggest that any beneficial action of the hormone on the toxemia of typhoid fever is a result of the action of cortisone on the host and not on the toxin itself.

In Part I of the present publication, Smadel and his colleagues⁶ have indicated that combined therapy with chloramphenicol and cortisone presents certain advantages over the chloramphenicol regimen previously employed. The present report is concerned with the clinical control of typhoid fever in seven patients by the use of cortisone alone. It may be mentioned immediately that the hormone, while producing obvious benefit to the patient, exerted no antibacterial effect and apparently did not significantly hasten the disappearance of *S. typhosa* from the patient.

METHOD OF STUDY

1. *Selection of Cases.* Seven patients, ranging in age from five to 45 years, were selected for treatment. All patients were proved to have typhoid

* Received for publication September 27, 1950.

From the Department of Medicine, School of Medicine, University of Maryland, Baltimore, and the Tropical Research Medical Laboratory, U. S. Army, San Juan, Puerto Rico.

This study supported by a grant from Parke, Davis and Company, Detroit, Michigan; the McCormick Company, Inc., Baltimore, and the Commission of Immunization of the Armed Forces Epidemiological Board.

The cortisone acetate in this study was supplied by Merck and Company, Rahway, New Jersey.

fever through isolation of *S. typhosa* from the blood, and the methods of study previously described² were employed in this series.

Three cases were treated in Puerto Rico, two in Baltimore, and two in Wilmington, Delaware, the latter through the coöperation of Dr. Lewis B. Flinn and Dr. William J. Holloway, of the Delaware Hospital, who treated cases 5 and 6.

2. *Laboratory Procedures.* Daily blood cultures were obtained during the pretreatment observation periods, and also daily for at least one week after beginning cortisone. The Widal reaction routinely employed gave positive results in all patients.

Stool and urine cultures were performed as frequently as feasible under the conditions of the study.

Blood cell counts were performed on all patients in the usual manner, but it was possible to follow the total eosinophil count in only two of the seven patients studied. Examination of the blood for sugar content was routine, but determination of serum chloride, sodium and potassium was accomplished in only two cases. Seventeen-ketosteroid output was not determined.

3. *Method of Administration and Dosage.* Cortisone acetate (Cortone*) was administered intramuscularly in all instances. In the four adult patients, cortisone was given in doses of 200 to 300 mg. for the first 24 hours, in divided doses of 100 mg. During the second 24 hours, 200 mg. were given to the adults and on the third day 100 mg. The children, aged 5, 7 and 11, were given approximately one-half the adult dose. One patient who relapsed received a second course of cortisone.

RESULTS

1. *Clinical.* In six patients the mean day of illness on which treatment was instituted was the eleventh. Illness in the seventh case was said to have been of 51 days' duration. Improvement in the patients' symptoms was uniformly observable and striking within the first 36 hours of therapy. Abatement of such symptoms as headache and mental dullness was definite within this time period. Two patients (cases 1 and 3) were moderately ill at the time treatment was instituted, and five were severely ill of whom one patient (case 5) was semi-comatose. Four of the seriously ill patients were markedly improved and able to eat, and expressed interest in their condition and surroundings within 24 hours after cortisone therapy was started. From this point on, the patients showed increased vigor and strength and convalescence progressed uninterruptedly until the relapse occurred in case 4. Details of the clinical findings are given with the accompanying charts and case reports.

2. *Fever.* The recorded data as to the effect on the febrile course constitute further striking evidence that cortisone influences the course of typhoid

* Trade name of Merck and Company, Inc.

fever. In six of the seven patients, irrespective of the height of the preceding fever, day of disease or age of the patient, cortisone therapy was followed by fall of temperature to normal levels within 100 hours after the initial dose; range 1 to 100 hours, average 36 hours. Normal temperatures were defined as rectal temperatures under 100° F. or oral temperatures under 99° F. In the fifth patient (case 5), the temperature became normal only after chloramphenicol therapy was instituted a week later.

3. *Effect on the Bacteremia.* Blood cultures from six patients contained *S. typhosa* prior to instituting therapy, while in the remaining case bacteremia was not demonstrated until relapse. In three patients blood cultures which had been positive immediately before treatment were negative the day following and remained so thereafter. In the other three cases who were positive before therapy, *S. typhosa* was isolated on the second, fourth and fifth days after beginning cortisone. From the seventh day after be-

TABLE I
Cortisone Treatment of Typhoid Fever

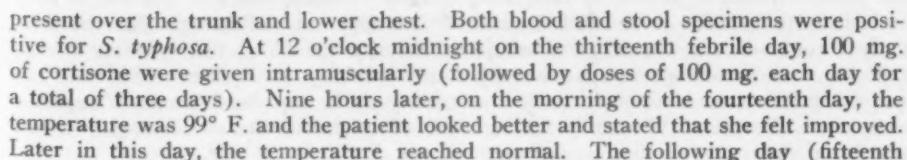
No.	Age	Sex	Wgt. Lbs.	Cortisone			Response After Treatment			<i>S. typhosa</i> Last Day Positive			
							Duration of Fever after Treatment (Hrs.)	Complications					
				Day of Disease Begun	Days Con- tinued	Total Drug (Mg.)		Nature	Onset. Day of Disease	Blood	Stool	Urine	
1	7	M	55	11	2	300	36	None			13	24	0
2	11	F	90	13	2.5	300	18	None			13	17	0
3	27	F	135	9	5	600	1	None			13	26	18
4	32	M	122	15	3	400	16	Relapse	25		26	24	0
5	45	M	120	51	3	700	No effect	Pericar- ditis	60		55	60	0
6	5	M	72	9	5	450	100	None			9	0	0
7	18	F	110	10	4	800	47	None			9	0	0

ginning therapy, in view of the patients' normal temperatures, blood cultures were not taken except in those instances (vide in figure) in which positive stool cultures were obtained. The two blood cultures taken because of this indication proved negative except in case 4 during his relapse.

4. *Effect on the Stool Culture.* Stool cultures were not obtained on any regular schedule. No patient was discharged, however, without three consecutive negative stool cultures having been recorded. Positive stool cultures after the termination of cortisone treatment were observed in five instances during convalescence, the longest remaining positive until the sixtieth day of disease, or six days after cortisone was stopped (case 5). Two patients (cases 6 and 7) showed consistently negative stool cultures for *S. typhosa*. Actually, as anticipated, cortisone showed no effect on the incidence of typhoid bacilli in the feces, since practically all patients demonstrated positive stools during the course of treatment.

7. *Complications.* Complications typical of typhoid fever, such as perforation and hemorrhage, were not encountered in the six cases first observed early in the course of disease. Patient 5, first diagnosed as typhoid fever and treated with cortisone on the fifty-first day of illness, experienced gross intestinal hemorrhage on the sixtieth day. The bleeding was not excessive and recovery was complete.

Case 2. The patient, an 11 year old Puerto Rican, was admitted to the hospital on the twelfth day of an illness characterized by fever with nausea, vomiting and diarrhea. Prior therapy had included penicillin, sulfadiazine and streptomycin and all had failed to alter the clinical condition. The patient was delirious and critically ill. The eyes were fixed and glassy, the facies was drawn and the abdomen moderately distended and tender, with a palpable spleen. Numerous rose spots were



day) the patient sat up in bed, she ate well, there was no abdominal pain or discomfort and the spleen was smaller. The patient was observed walking about the ward on the next day. Progressive improvement was noted from this point onward. The febrile course and pertinent laboratory findings are presented in figure 1.

Case 3. (Pregnancy complicated by typhoid fever). The patient, a 27 year old colored female, entered the University Hospital, Baltimore, on the third day of an illness characterized by fever of 103° F., headache, abdominal pain, cough and malaise. The patient, a para 5-0-0-5, was approximately 18 weeks pregnant. On examination, she was oriented but acutely ill and somewhat dyspneic. The skin was hot and dry and small macular lesions were noted, particularly on the trunk. Râles were heard posteriorly in the right lung and also in the extreme left base. Cardiac sounds were normal. In addition to the gravid abdomen, there was rather diffuse abdominal tenderness. Physical examination was otherwise normal. Specimens of blood were positive for *S. typhosa* on the third and fifth days of illness, and a

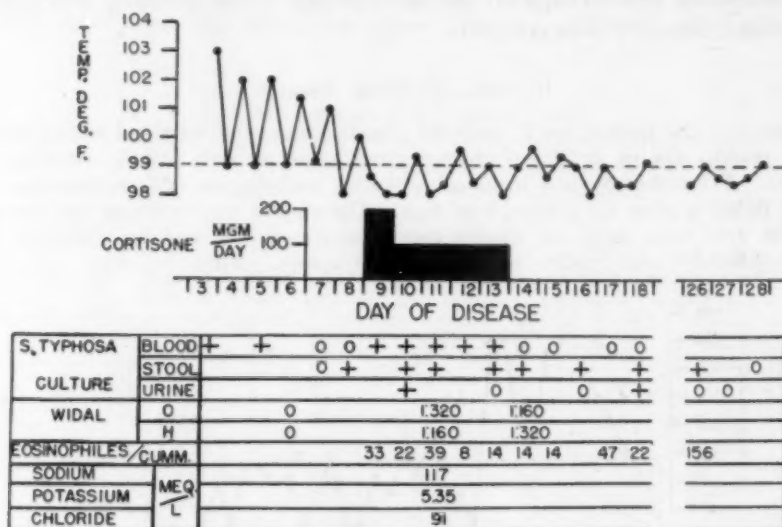


FIG. 2. *Case 3.* Typhoid fever. Course of disease in a 27 year old pregnant patient. Bacteremia present for five days during cortisone treatment.

specimen of stool was positive on the eighth febrile day. For several days the headache, toxemia and cough remained unabated, but on the seventh day the appearance of the patient was improved without the use of any type of specific therapy. At mid-day on the ninth day of disease it was decided to use cortisone in spite of the apparent improvement. Accordingly, the patient received 100 mg. of cortisone twice on the ninth day, and subsequent doses of 100 mg. daily for an additional four days. From the day that cortisone was first given there was no temperature rise and the patient remained absolutely free of symptoms. Indeed, she was difficult to keep in bed under isolation precautions because of her apparent well-being. Nevertheless, daily throughout the five days of cortisone therapy the blood was positive for *S. typhosa*, first becoming negative on the fourteenth day of disease. The stool remained positive intermittently until the twenty-sixth day but remained negative thereafter. Pertinent laboratory findings, including the results of eosinophil counts and blood electrolyte studies, are given in figure 2.

We consider this case most interesting from two aspects: First, the course of the disease in this pregnant patient seemed milder than one would have expected from the typhoid infection. The possibility was considered that the patient was already enjoying a high degree of adrenal stimulation as a result of pregnancy and that this may have contributed to the mildness. We were not able to perform 17-ketosteroid assays and confirm the existence of such stimulation. On the other hand, typhoid fever can be a disease of variable severity and duration.⁷ Second, the patient remained free of symptoms in spite of a persistent typhoidal bacteremia for five days.

Case 4. (Patient with relapse after cortisone.) The patient, a 32 year old Puerto Rican male, was admitted to the hospital on the ninth day of an illness characterized by fever, abdominal pain, loose bowel movements, headache and weakness. Temperature during the five days prior to beginning therapy ranged from 98° to 102.2° F. On the fifteenth febrile day it was 101.5° F. At this time the patient was

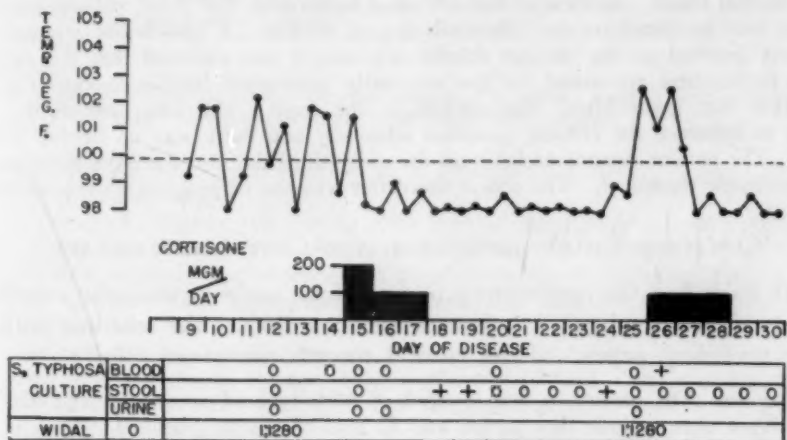


FIG. 3. Case 4. Typhoid fever. Graphic record of a patient who relapsed after cortisone treatment. Recrudescence symptoms responded rapidly on re-administration of cortisone.

lethargic and toxic. The tongue and gums were dry, and the spleen was readily palpable 2 fingerbreadths below the costal margin. On the fifteenth day the patient received 200 mg. of cortisone as an initial dose and subsequent doses of 100 mg. each day for two additional days. Within 16 hours after beginning hormone therapy, the temperature reached normal levels and the patient stated that he felt stronger and better. On the second treatment day he was decidedly improved and had gained in both strength and appetite. The abdominal discomfort and diarrhea had subsided. For the first time, however, the stools became positive for *S. typhosa* on the eighteenth and nineteenth days of illness and again on the twenty-fourth day. The course of the disease was otherwise uneventful until the twenty-fifth day, when there was a return of fever, headache, abdominal pain and splenomegaly. A blood culture on the following day was positive for *S. typhosa*. Later on the twenty-sixth day, or approximately 24 hours after the relapse began, the patient received 100 mg. of cortisone and a similar dose daily for three days. Within 12 hours, the temperature dropped from 102.6° F. to 97° F., and within this period he felt subjectively im-

proved and complained of no discomfort. Following the rapid defervescence, the patient manifested no evidence of illness with the exception of the splenomegaly, which did not recede until about the thirty-third day of disease. The pertinent findings are presented in figure 3.

Case 5. The patient, a 45 year old colored male, first came under observation in the Delaware Hospital, Wilmington, on about the fiftieth day of a febrile illness. The patient, critically ill at this stage of disease, was extremely toxic, dehydrated and disoriented. Numerous râles were heard in both lungs, the spleen was readily palpable, and the afternoon temperature was 104° F. Bacteria identified as *S. typhosa* were obtained from the blood on the fifty-first day of illness. On this day 300 mg. of cortisone were given in divided doses of 100 mg., and then 200 mg. daily for two days. On the following day, less than 24 hours after therapy was instituted, the patient conversed coherently, appeared to be decidedly stronger, and fed himself in bed. Dr. Lewis B. Flinn stated that he had never observed such remarkably rapid improvement in a typhoid patient so seriously ill. In spite of the improved clinical condition, the blood cultures remained positive until the fifty-fifth day of disease and the stools were positive until the sixtieth day; furthermore, the temperature did not reach normal levels. In view of the continued bacteremia and fever, chloramphenicol therapy was instituted on the fifty-sixth day of disease. A pericardial friction rub was first detected on the sixtieth febrile day, and it was assumed that the complicating pericarditis accounted for the unusually protracted febrile course. On the sixty-first day, gross blood was noticed in the feces. The complication did not appear to influence the clinical condition adversely and there was no further recurrence. The patient became afebrile on the sixty-third day, or six days after beginning antibiotic treatment. The course thereafter was one of progressive improvement.

COMBINED CHLORAMPHENICOL AND CORTISONE THERAPY

We have had the opportunity to treat four patients with the combined therapy of chloramphenicol and cortisone according to the schedule outlined in the preceding paper.⁹ Brief clinical records are given below:

Case 1a. The patient, a female aged 58 with typhoid fever, received 350 mg. of cortisone over a three day period and 32 gm. of chloramphenicol over a period of 10 days. The response to this treatment was striking, with improvement of the clinical condition within 24 hours after instituting treatment and return of temperature to normal levels in 48 hours. Blood cultures were negative for *S. typhosa* after beginning treatment. A relapse of symptoms with bacteremia occurred on the forty-second day of disease but responded satisfactorily to readministration of chloramphenicol.

Case 2a. A 13 year old girl seriously ill with typhoid fever received 600 mg. of cortisone during three days in combination with 20 gm. of chloramphenicol administered during 10 days. When treatment was first instituted the temperature was 106.4° F. and abdominal pain and distention were marked. Within 12 hours after beginning treatment there were striking changes in the clinical condition and in 24 hours the temperature had reached normal levels. Pertinent clinical and laboratory findings are presented in figure 4.

Case 3a. A 10 year old negro female child received cortisone and chloramphenicol simultaneously on the ninth day of typhoid fever. Over a period of 4 days 450 mg. of cortisone were given and 12 gm. of chloramphenicol were administered for 10 days. The patient was noticeably improved within 18 hours after beginning treatment and the temperature reached normal levels in 24 hours. Neither blood

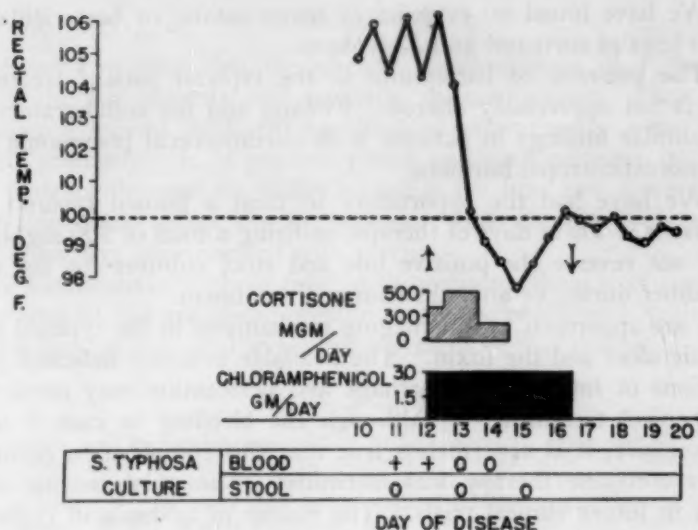


FIG. 4. Case 2a. Typhoid fever. Graphic record of a patient treated with cortisone and chloramphenicol. Note rapid defervescence.

nor stool cultures were found positive for *S. typhosa* after therapy began. The further course was uneventful.

Case 4a. A 63 year old woman with typhoid fever received chloramphenicol on the sixth day of the disease. Although the patient was not regarded as seriously ill there was no noticeable improvement after 48 hours of antibiotic therapy. Accordingly treatment was supplemented with cortisone on the eighth day of illness. Twelve hours later the temperature reached normal levels and the patient appeared clinically well. A total of 700 mg. of cortisone was administered in three days in addition to the 36.5 gm. of chloramphenicol given in 14 days. Blood cultures for *S. typhosa* were negative after the eighth day of disease although stool specimens were intermittently positive until the thirty-first day. A typhoidal relapse occurred on the thirty-third day which responded promptly on readministration of chloramphenicol.

DISCUSSION AND SUMMARY

There is abundant evidence, particularly exemplified by publications of Selye,⁸ that adrenal cortical hormones play a fundamental part in modifying the alarm mechanism of the host under varying conditions. His work and that of others have suggested that the host cell may be helped to survive varying embarrassing situations and, for a time at least, be made impervious to outside attack.

Research throughout the past few decades has been on antimicrobial aspects of infection aimed at either destroying or inhibiting the bacterial invaders. Now with ACTH and cortisone available, opportunities are at hand for evaluation of the host factor in various types of infections. That cortisone has no direct action on the typhoid bacillus is exemplified in several ways:

(1) We have found no evidence of bacteriostatic or bactericidal effect in *in vitro* tests of cortisone and *S. typhosa*.

(2) The presence of bacteremia in the typhoid patient treated with cortisone is not appreciably altered. Finland and his collaborators⁸ have reported similar findings in patients with pneumococcal pneumonia treated with adrenocorticotrophic hormone.

(3) We have had the opportunity to treat a known typhoid carrier with cortisone. Three days of therapy, utilizing a total of 500 mg. of cortisone, did not reverse the positive bile and stool cultures for the typhoid bacillus, either during or after the course of treatment.

There are apparently two damaging mechanisms in the typhoid patient: the necrotic ulcer and the toxin. The available evidence indicates that the complications of intestinal hemorrhage and perforation may occur despite chloramphenicol treatment.^{1,2} Although the bleeding in case 5 was not unduly excessive, it is nevertheless true that this complication occurred 10 days after cortisone therapy was instituted. The point merits full consideration in future clinical trials. The matter of toxemia in typhoid, dependent upon the liberation of toxin from the pathogenic bacteria present in the host, represents another and presumably a paramount factor to cope with.

Smadel and his collaborators⁶ have presented evidence that chloramphenicol treatment of typhoid fever, supplemented with cortisone, results in a more prompt clinical response than was formerly observed with antibiotic treatment alone.^{1,2} The results in the four patients whom we have treated with such combined therapy and reported briefly in this paper confirm their findings.

Cortisone, lacking any direct antibacterial effect and probably possessing no direct effect on the toxin of *S. typhosa*, is surmised to have acted through its effect on the host. In all of the seven typhoid patients that we treated with cortisone alone during the acute stages of disease, there was uniform improvement of the clinical condition. In five instances, cortisone single-handedly controlled the clinical infection, including a second administration of the hormone to one patient who had relapsed. Two patients eventually received chloramphenicol, because of persistent positive stool cultures in two instances, and because of continued fever in one instance which was thought to have been caused by a complicating pericarditis. In all patients there was definite bedside improvement within 24 hours, irrespective of the severity of illness at the time of beginning treatment.

It appears, therefore, that cortisone does exert a favorable influence upon the host during the course of typhoid, and further study may confirm our impression and that of Smadel and his group⁶ that cortisone may serve as an ancillary aid to chloramphenicol in the management of this enteric disease. It is apparent that additional clinical evaluation is essential to determine whether cortisone might lead to any unwanted physiologic or structural alterations during the course of typhoid fever.

CONCLUSIONS

Cortisone has controlled the clinical manifestations of typhoid fever completely in six patients and partially in one patient. Four typhoid fever patients treated with chloramphenicol concurrently with cortisone responded promptly. It is presumed that cortisone achieves its effect in typhoid patients through its ability to assist the host cell, since it has no demonstrable direct effect on *S. typhosa*. One chronic typhoid carrier failed to show any improvement with cortisone.

While treatment of typhoid fever with cortisone alone is of considerable theoretic interest, we are of the opinion that chloramphenicol, with its anti-bacterial action, is still vital in the management of this disease.

ACKNOWLEDGMENTS

The authors wish to express appreciation to Dr. Lewis B. Flinn and Dr. William J. Holloway, Wilmington, Delaware, and to members of the pediatric and medical staffs of the University Hospital, Baltimore, and the Municipal and Bayamon District Hospitals, San Juan, Puerto Rico, for their care in the clinical management of several cases. Mr. Merrill J. Snyder, M/Sgt. Robert Helmhold, Miss Ann Merideth, Miss Audrey M. Funk and Miss G. Ann Gamber contributed technical assistance. The coöperation of the Medical Art Department, University of Maryland, is appreciated.

BIBLIOGRAPHY

1. Woodward, T. E., Smadel, J. E., Ley, H. L., Jr., Green, R., and Mankikar, D. S.: Preliminary report on the beneficial effect of chloromycetin in the treatment of typhoid fever, *Ann. Int. Med.* **29**: 131, 1948.
2. Woodward, T. E., Smadel, J. E., and Ley, H. L., Jr.: Chloramphenicol and other antibiotics in the treatment of typhoid fever and typhoid carriers, *J. Clin. Investigation* **29**: 87-99, 1950.
3. Smadel, J. E., Woodward, T. E., and Bailey, C. A.: Relation of relapses in typhoid to duration of chloramphenicol therapy, *J. A. M. A.* **141**: 129, 1949.
4. Lewis, L. A., and Page, I. H.: Studies on the protective power of adrenal extract and steroids against bacterial toxins in adrenalectomized rats. Appendix 1 to: Kendall, E. C., *The Chemistry and partial synthesis of adrenal steroids*, *Ann. New York Acad. Sc.* **50**: 547, 1949.
5. Jackson, E. B., and Smadel, J. E.: Cortisone and ACTH on toxins of rickettsial and *Salmonella typhosa*, *Bact. Proc.*, pp. 92-93, 1950.
6. Smadel, J. E., Ley, H. L., Jr., and Diercks, F. H.: Therapy of typhoid fever. Part I. Combined therapy with cortisone and chloramphenicol, *Ann. Int. Med.* **34**: 1-9, 1951.
7. Green, R.: An epidemic of typhoid fever, in: *Annual report of the Institute for Medical Research for 1939*, published by Federated Malay States Government Press, 1940, p. 25.
8. Selye, H.: The general adaptation syndrome and the diseases of adaptation, *J. Clin. Endocrinology* **6**: 117, 1946.
9. Finland, M., Koss, E. H., and Ingbar, S. H.: Effects of ACTH in primary atypical (viral) pneumonia and in pneumococcal pneumonia (preliminary report), Chapter 45 in: Mote, J. R.: *Proceedings of the first clinical ACTH conference*, 1950, Blakiston, Philadelphia, p. 529.

EPIDIDYMITIS IN MUMPS, INCLUDING ORCHITIS: FURTHER CLINICAL STUDIES AND COMMENTS *

By SAMUEL CANDEL, M.D., F.A.C.P., *Brooklyn, New York*

ORCHITIS is a significant and common complication of mumps occurring after puberty. On the other hand, epididymitis as a frequent concomitant of the orchitis of mumps apparently has escaped the attention of many observers. Candel, Wheelock and Grimaldi¹ observed a case of mumps in which bilateral epididymitis preceded the appearance of bilateral orchitis by two days. This focused their attention upon the epididymis, and they concluded from a study of 105 cases of mumps, of which 23 developed orchitis, that epididymitis is frequently associated with orchitis. They felt that this was worth recording for two reasons: (1) All of the pertinent available texts at the U. S. Naval Dispensary, Gulfport, Mississippi, either made no mention of epididymitis in mumps or considered that it was a rarity. (This will be discussed in more detail later when a more extensive survey of current texts will be taken up.) (2) Many of the very competent physicians, including two excellent urologists, with whom the writers had the honor of serving, likewise were of the opinion that epididymitis did not occur or was rare.

It is of interest to record that in 1909, Waddelow² reported a case of mumps, similar to the one mentioned above, in which epididymitis preceded orchitis by at least one day. Feiling³ described a like experience in 1914. Five cases are cited in the literature in which only the epididymis was involved.⁴

There has been, necessarily, a paucity of material available for pathologic study. In 1912, Smith⁵ treated by operation two cases of orchitis due to mumps. At operation he found the epididymis definitely enlarged, soft and deep red, and stated that it showed a picture of acute congestion. He secured a small piece for biopsy. Dr. S. B. Wohlbach, who did the microscopic study, observed that the inflammatory process spread partly by extension along the tubules to the epididymis. He commented that this was of interest since several writers had held that the process affected the epididymis first and the testicle secondarily. Therefore, what pathologic material is available indicates that epididymitis is a fact.

In 1945, the author studied more intensively 224 additional cases of mumps. Sixty-eight of the 224 were complicated by epididymitis and orchitis. Twelve showed bilateral gonadal involvement. The charts of

* Received for publication December 28, 1948.

From the U. S. Naval Training Center, Gulfport, Mississippi.

The views expressed herein are the opinions of the writer and not necessarily the views of the Bureau of Medicine and Surgery or the Navy at large.

two patients did not contain enough data regarding detailed clinical findings. Thus 66 cases of orchitis, 12 of which were bilateral, were studied carefully. Of the 78 involved gonads, all exhibited the classical signs of inflammation, pain, tenderness, and very frequently swelling. It should be noted that, while most often it is not too difficult to identify the epididymis when epididymo-orchitis occurs, sometimes it is very difficult in a markedly swollen gonad. Under such circumstances, daily palpation will eventually reveal the outlines of these two separate structures. As the inflammatory process begins to subside, the consistency of the testicle soon varies from that of the epididymis. One obtains the impression that the swelling of the testis is subsiding a little more rapidly than the swelling of the epididymis. A similar observation was first made by M. Sorel,⁶ of the French Army, in 1877.

Of the 78 involved gonads, 67 (85 per cent) showed inflammation with enlargement of the epididymis. In some instances the swelling was relatively enormous. Table 1 records the extent of the enlargement of the epididymis at the height of the inflammatory process.

TABLE I

Enlargement of Epididymis at Height of Inflammation	No. of Cases
None	11
Slight	18
2 to 4 times normal	44
6 to 12 times normal	5

On discharge, 19 cases showed enlargement and nonpainful thickening of the epididymis. Table 2 records the extent and frequency of that enlargement.

TABLE II

Enlargement of Epididymis on Discharge	No. of Cases
None	55
Slight	5
2 times normal	14
Not recorded	4

Edema and tenderness of the funiculus of the involved gonad have been observed in mumps. Of the 78 gonads under study, 63 showed edema of the funiculus. Eleven showed no edema. Four were not recorded. In 13 instances there was marked tenderness of the funiculus, a manifestation of a funiculitis. The duration of this edema of the funiculus was recorded in 48 instances. Nine lasted one week or less. Thirty-one lasted one to two weeks. Eight lasted two to three weeks.

In addition to the problem of epididymitis, a number of clinical features of the complication of epididymo-orchitis were studied and recorded, for no ready reference to them is to be found either in texts or in the literature. Lack of appreciation of the clinical course of the untreated disease led

Rambar⁷ to state that pooled plasma given intravenously caused a dramatic defervescence of temperature and symptoms in two cases of mumps orchitis. Candel et al.¹ questioned the value of these criteria and pointed out that, of 17 of their own observed cases of mumps orchitis, nine terminated by crisis and eight by lysis over a two to three day period. Candel et al. also stated that an amelioration of local symptoms always went hand in hand with the defervescence of temperature. In a later paper Rambar,⁸ who repeated his experiment (however, this time utilizing controls), reversed his stand and wrote: "The value of serum or plasma as a therapeutic procedure cannot be definitely demonstrated." Smith⁹ likewise wrote of the dramatic response of five cases of orchitis to pooled plasma. He too was led to an erroneous conclusion because of lack of controls.

Orchitis and epididymitis as complications of mumps are rare before puberty. In a previous study of 2,368 men who were questioned, 1,122 gave a history of mumps. Forty-nine of them had been complicated by

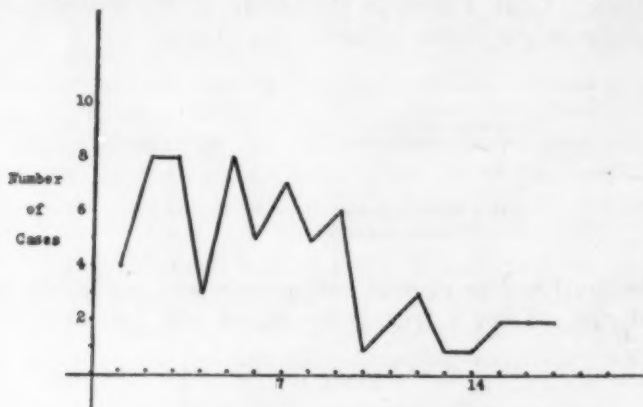


FIG. 1. Day of appearance of epididymo-orchitis.

epididymo-orchitis. No case had occurred under 10 years of age. One occurred at 10 years of age. Forty-eight occurred at the age of 12 or over. Epididymo-orchitis can occur before, coincidental with, or without parotid swelling.^{1, 3, 10, 11, 12, 13, 14, 15}

Of the 224 cases with which this paper primarily concerns itself, 68 developed epididymo-orchitis. Sixty-six per cent of these occurred in the first week; 25 per cent occurred in the second week, and 9 per cent in the third week of the disease. Figure 1 is a graph noting the frequency of occurrence of the complication by day of disease.

Of 66 cases of epididymo-orchitis, 12 showed bilateral involvement. All of the testes exhibited signs of inflammation, i.e., tenderness, pain, swelling or induration. The author wishes to call attention to an occasional patient who will complain of testicular pain which may last for some hours and yet never develop any objective sign of local disease. No such case was in-

cluded in this series. This phenomenon has been observed before and recorded by Catrin¹¹ and Radin.¹²

Table 3 records the extent of enlargement of the testis as compared to the normal in orchitis of mumps origin.

TABLE III

Enlargement of Testis	No. of Gonads
None	8
Slight	20
1.5 times normal	18
2 times normal	19
3 times normal	12
4 times normal	1

Table 4 shows the duration of physical signs of swelling, pain and tenderness. Pain and swelling were the first phenomena to disappear fairly promptly after defervescence of temperature. Tenderness was the last to go. This residual tenderness, most often only very minimal, persisted sometimes for many days after marked swelling and pain were gone. Table 4 outlines the duration of signs of inflammation, including the disappearance of the last sign to be present, i.e., minimal tenderness.

TABLE IV

Duration of Signs of Inflammation

No. of Days	Frequency
3-5	9
6-10	34
11-15	20
16-20	9
21-25	6

Table 5 is a résumé of the highest oral temperature recorded in each of 66 cases of epididymo-orchitis. Seventeen of these patients had marked chills associated with the fever.

TABLE V

Epididymo-Orchitis

Highest Oral Temperature in Degrees Fahrenheit	Frequency
98.6-99	4
99.2-100	6
100.2-101	1
101.2-102	12
102.2-103	13
103.2-104	18
104.2-105	11
105.2-106	1
	<hr/> 66

Table 6 notes the duration of fever (attributable to orchitis and epididymitis) in days, and the frequency. Four cases are not included, since the temperature ranged from 98.6° to 99° F. orally.

TABLE VI

Duration of Fever No. of Days	No. of Cases
1	2
2	3
3	9
4	20
5	18
6	5
7	5
	<hr/> 62

It can be seen that of these 62 cases, 22.5 per cent had fever three days or less, 54.8 per cent had fever for four days or less, and 83.8 per cent had fever for five days or less. All of our cases in this study had fever for not more than seven days. However, in a previous study Candel et al.¹⁶ recorded one case in which fever lasted for nine days.

The manner of defervescence of temperature was investigated. Of the 66 cases, 11 were excluded because the highest temperature recorded in them was 100.2° F. orally. Fifty-five cases remained whose highest temperature in the febrile period, due to epididymo-orchitis, was 101.2° F. or more. Table 7 records these cases.

TABLE VII

Manner of Subsidence of Temperature

Manner	No. of Cases
Crisis	28
Lysis—within 48 hours	4
Lysis—within 72 hours	17
Lysis—within 96 hours	6

Thus, in the febrile period due to the gonadal complication, approximately 50 per cent of all cases terminated by crisis without any therapy. In a previous communication we pointed out that nine out of 17 similar cases terminated by crisis. It is evident, then, when the two cases⁷ mentioned above which were treated by pooled plasma given intravenously showed a prompt defervescence of temperature, it did not necessarily follow that the particular therapeutic procedure was of value, since the fever in 50 per cent of all cases of epididymo-orchitis terminates spontaneously by crisis.

It was evident clinically that there was some correlation between the size of the testicular swelling and the systemic reaction of fever. In a general way, minimal involvement of the testicle was apt to be associated with less fever and less severe systemic symptoms. Of those cases with swelling 1.5 times normal or less, the relationship of the groups with fever over 102° F. to those with fever under 102° F. was approximately 1:1. If the swelling of the gonad was two to four times normal, the relationship of the groups with fever over 102° F. to those with fever under 102° F. was approximately 6:1. Table 8 demonstrates that relationship.

TABLE VIII

Size of Testicle	More than 102°	Highest Temperature Oral 102° or Less	Ratio Approximately
(a) 1.5 times normal or less	17	19	1:1
(b) 2 to 4 times normal	26	4	6:1

Upon discharge, all patients were examined to determine the state of the involved testes. The most prominent sign of residual affection of the gonad was loss of turgor of the testicle. Table 9 records our findings.

TABLE IX

Consistency of Testes on Discharge	No. of Testes Examined
Normal	43
Loss of turgor	35

Of these 78 testes, 44.9 per cent showed loss of turgor. In two cases a slight decrease in the size of the testicle was noted, while in two other cases the testes showed atrophy to one half the size of the normal. In a previous study we¹ demonstrated that, of 49 cases of mumps orchitis which were examined several years after occurrence of the complication, loss of turgor and atrophy were demonstrable in 27 of the testes (55 per cent). Of these, nine were atrophied to approximately one-third normal, 12 were one-half normal, and six were two-thirds normal. Since in the present study, aside from loss of turgor, only four cases showed any atrophy immediately upon discharge, it is reasonable to assume that the process of atrophy is a progressive one and that the process continues after the patient with the epididymo-orchitis is clinically symptom free and discharged from medical care.

There is much confusion in current and relatively recent texts on urology, internal medicine and contagious disease as to the frequency or even the very occurrence of epididymitis in association with the orchitis of mumps. One author¹⁷ states that the epididymis is never involved; five^{18, 19, 20, 21, 22} say that epididymitis is rare; eight^{23, 24, 25, 26, 27, 28, 29, 30} write that the epididymis may be involved; five^{31, 32, 33, 34, 35} mention that epididymitis does occur and imply that this is relatively frequent; 13^{36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48} writers ignore the question entirely and omit any mention of epididymitis in mumps. Our own experience has shown us a definite inflammation and swelling of the epididymis in 85 per cent of our cases. The other 15 per cent showed no enlargement, but some showed tenderness and induration, while in others we could not be certain that no inflammatory process was present even though we observed no swelling or noted no tenderness in them.

. Significant observations have been made on epididymitis in mumps. They have appeared in the literature but have been overlooked, for the most part, by many writers. In 1832 and 1853, Trousseau⁴⁹ noted two cases of mumps orchitis associated with epididymitis. In 1876, Boutelle⁵⁰ described nine such cases. Sorel,⁵ writing in 1877, concluded that epididymitis

preceded the orchitis in 12 cases of mumps. Seventeen years later, Catrin¹¹ studied 43 cases of mumps orchitis, of which 12 were bilateral, and confirmed the findings of Sorel. We quote the following from Catrin because the pointedness of his remarks is as valid today as 50 years ago: "It is known that most authors have emphasized the absence of participation of the epididymis in mumps orchitis. Absence of epididymitis has even been mentioned as a classic sign in differentiating mumps orchitis from gonorrheal orchitis. It is well to recognize that, in spite of the many findings to the contrary which we will mention, authors pass this error from hand to hand and in more recent treatises often cite the immunity of the epididymis in mumps orchitis." The papers of Sorel and Catrin are particularly commended to the reader because of the wealth of fine clinical observations on gonadal involvement in mumps. The following observers have reported epididymitis in mumps orchitis: Waddelow,² Phillips,⁵¹ Feiling,⁸ Radin,¹² Wesselhoeft,⁵² Zax,⁵³ Candel, Wheelock and Grimaldi,¹ and Zax.⁵⁴

In 1945 we made a survey of cases which were admitted to the sick bay with diagnoses of acute nonvenereal orchitis or epididymitis during the preceding year. As these patients were admitted originally to the urologic service, we had no opportunity to examine them personally. It was always our suspicion that many of the cases so diagnosed, where no etiologic factor was demonstrable, were cases of epididymo-orchitis secondary to systemic mumps in which the parotitis was missed clinically or in which the salivary glands were never involved. Much of our studies in mumps was devoted to the establishment of criteria to make the diagnosis under such conditions.^{1, 55}

In 1821 Hammersley⁵⁵ observed an epidemic of mumps in a New York prison. There were 80 cases, of which 17 developed orchitis. Six of these 17 showed no parotitis. If these six cases had been discovered elsewhere, without the knowledge that they had been exposed to mumps, they could almost certainly have been designated as acute nonvenereal orchitis. Wesselhoeft⁵² collected 64 such cases from the literature. Phares,⁵⁶ in 1813, in civilian practice in Mississippi, described an epidemic of mumps in which he saw 30 cases of orchitis. He noted that in the same period he saw other cases of orchitis, caused neither by metastases (mumps) nor gonorrhea. Still other cases of similar nature were reported to Phares by his colleagues. Some amusing etiologic factors were entertained to be the cause of this type of orchitis, such as: (a) young man being teased by a bride; (b) wearing of tight pants and walking along a railroad; (c) following horse back riding. Phares' cases, too, would fit the designation of orchitis, acute nonvenereal, but in all likelihood they were secondary to mumps.

In 1944, 27 cases were admitted to the urologic service with diagnosis of orchitis or epididymitis, acute nonvenereal. Six were eliminated from consideration because of apparent etiologic factors. Of these six, two were

secondary to direct trauma, two had episodes of recurrent epididymitis, one had had urinary symptoms for two weeks previous, one had orchitis and syphilis. Thus, 21 cases remained in whom no etiologic factor was ascertainable. During that same year 131 cases of mumps were seen and these were complicated by 27 instances of epididymo-orchitis.

Table 10 shows the frequency of occurrence of mumps, mumps epididymo-orchitis, and acute nonvenereal orchitis and epididymitis in quarterly periods.

TABLE X

	Mumps	2° Epididymo-orchitis	Orchitis and Epididymitis Acute Nonvenereal
Jan.-March	49	9	7
April-June	61	14	8
July-Sept.	13	4	4
Oct.-Dec.	8	0	2

It can be seen from table 10 that in the first six months of the year, when the incidence of mumps was highest, there were more cases of orchitis and epididymitis acute nonvenereal admitted to the urologic service than in the last six months of the year, when the incidence of mumps was lowest. This certainly suggests that some if not all of the cases designated as acute nonvenereal orchitis and epididymitis might have been of mumps origin.

The diagnosis of epididymo-orchitis due to mumps may be very simple, but it may also be very difficult. When parotitis or swelling of the submaxillary or sublingual glands appears shortly before or concomitant with the gonadal complication, the diagnosis is easy. If the epididymo-orchitis is present alone, or if it precedes the salivary gland swelling, the diagnosis is more difficult. Under such circumstances, the following are aids in the diagnosis:

- (1) History of contact with a case of mumps.
- (2) The presence of evidences of an associated meningitis, either (a) clinical meningitis with nuchal rigidity, headache, etc., or (b) subclinical meningitis, as evidenced by an increased number of cells in the spinal fluid.^{87, 18}
- (3) If parotid gland involvement was present before the appearance of epididymo-orchitis, but was not detected clinically, the serum may show elevated amylase values.^{88, 89}
- (4) Complement fixation test for mumps antibody, as described by Enders et al.⁹⁰
- (5) Skin test for dermal hypersensitivity which becomes positive after recovery from mumps.⁹⁰

Once epididymo-orchitis has appeared, treatment is purely symptomatic, with rest in bed, elevation of the testis by means of a bridge, application of an ice bag, and codeine sulfate and salicylates for the relief of pain. The

patient may be permitted out of bed after his temperature has returned to normal and all evidence of inflammation is gone.

The logical approach to the problem of the treatment of the complications of mumps lies, of course, in the field of preventive medicine. Studies have been carried out by Stokes et al.⁶¹ which have demonstrated that vaccination with a formol inactivated virus of mumps has been able to confer a significant degree of immunity against mumps. Thus, mass prophylaxis of mumps by means of vaccination may become a possibility when such a vaccine is finally developed. Whereas in civilian practice this may not be of great importance, in military medicine, where mumps is a common disease and epididymo-orchitis complicates 20 per cent or more of cases, such prophylaxis would be of inestimable value.

Once mumps has appeared clinically, the problem of preventing the gonadal complications has been attacked by attempting to introduce, passively, large amounts of mumps antibody into the affected patient. De Lavergne and Florentine,⁶² Teissier,⁶³ and Hinckley⁶⁴ reported a reduction in the incidence of orchitis as a complication of parotitis in patients treated with convalescent serum. Bailey and Haerem⁶⁵ found that convalescent serum prepared from patients who had developed orchitis was more effective than serum obtained from uncomplicated mumps convalescents. Enders⁶⁶ showed that mumps antibodies were present in human gamma-globulin preparations in concentrations 25 times greater than in pooled plasma. Candel et al.¹ demonstrated that 100 c.c. of pooled plasma given intravenously were of no value as a prophylactic measure in preventing mumps orchitis, and inferred that this amount of plasma did not contain enough antibody. Gellis et al.⁶⁷ determined that 20 c.c. of gamma globulin prepared from mumps convalescent serum injected intramuscularly markedly reduced the incidence of orchitis as a complication of mumps. Indeed, the incidence of orchitis in their treated group was 7.8 per cent, as compared to 27.4 per cent in a control group. Gellis and his co-workers found that 50 c.c. of gamma-globulin prepared from pools of normal human plasma were ineffective in reducing the incidence of orchitis complicating mumps. Candel,⁶⁸ however, found that 50 c.c. of gamma-globulin, obtained from normal pooled plasma and injected intramuscularly (in 25 c.c. doses 24 hours apart), appeared to have an effect in reducing the incidence of the complication. He concluded that further study was necessary. Nevertheless, there can be no question that gamma-globulin prepared from mumps convalescent serum should be the more effective preparation, since the antibody content of gamma-globulin prepared from mumps convalescent serum is 10 times greater than that prepared from pooled plasma.⁶⁹

Savran⁷⁰ utilized diethylstilbestrol to prevent orchitis in patients affected with mumps. He gave 4 mg. daily for five days, and indicated that it was of value in reducing the incidence of orchitis. His treated group showed 3.9 per cent complicated, as compared with 16.9 per cent in the control

group. These figures represent the incidence of orchitis when all the cases of orchitis present on admission were excluded from both series. However, according to Savran's own table, when these cases were not discarded the incidence of orchitis is 18.2 per cent in the treated group as compared to 25.5 per cent in the untreated. Seventeen other cases were discarded from consideration in the treated group because a temporary shortage of diethylstilbestrol enabled them to receive only partial treatment. Of these 17, four had orchitis on admission and five developed the complication later. According to our own calculation, if these 17 are added to the treated group, the incidence of orchitis in the treated group was 24.4 per cent (23 cases of orchitis in 94 cases of mumps), as compared to 25.5 per cent in the untreated group (43 cases of orchitis in 168 cases of mumps). The difference between the two groups thus vanishes. One would, therefore, need more convincing evidence before accepting the conclusion that diethylstilbestrol is of value.

It was pointed out above that pooled plasma was of no value in the treatment of a full blown case of orchitis. Sorel⁶ in 1877 wrote: "From the point of view of treatment, that which one must look for is a way of preventing the partial atrophy of the testicle. As to the duration itself of the affection, one comprehends that in a disease whose duration is so short, the most diverse treatments are followed by successes, above all if the treatment is given the day of acme of the disease."

From time to time, advocates of the surgical treatment of mumps orchitis have appeared in the literature. Two of the most recent of these have been Nixon and Lewis,⁷¹ who reviewed the literature on the surgical treatment of orchitis in mumps and added their own experiences. They quoted that Henry Smith in 1864 advised multiple punctures of the tunica albuginea; Schottmüller in 1904 recommended incision through the tunica vaginalis to release the hydrocele fluid; George Smith in 1912 incised the tunica vaginalis and made multiple incisions in the tunica albuginea; Ballenger and Elder in 1920 made an H-shaped incision in the tunica albuginea, and Wesselhoeft and Vose in 1942 utilized a similar procedure. Nixon and Lewis, who felt that Wesselhoeft and Vose's technic was a little too radical to be done routinely, decided to test whether simple drainage of the hydrocele fluid might give equally satisfactory results. This procedure was performed on 66 patients. They found that the temperature due to orchitis returned to normal on an average 2.1 days after operation. Some temperatures returned to normal in 24 hours, others as late as five days after operation. Since the authors do not give the average day of disease (orchitis) on which the 66 cases were operated on, the statement that the temperature returned to normal on the average of 2.1 days after operation lacks full meaning. The temperature charts (Nixon and Lewis) of three illustrative cases show that in figure 4, the patient was operated on on the second day of orchitis and had a normal temperature on the third day; figure 5 shows a patient

operated on on the third day of orchitis with a normal temperature on the seventh day; figure 6 shows a patient operated on on the third day with normal temperature on the fifth day. Our own studies of the normal sequence of events in orchitis show that on the third day 22.5 per cent of patients show a normal temperature, and that on the fifth day 83.8 per cent of patients show a normal temperature. It was also shown that normally approximately 50 per cent of our cases of orchitis subsided by crisis. A subsidence of temperature within 24 hours after an operative procedure would not necessarily mean that the operative procedure was responsible for the return of temperature to normal. In all febrile patients with orchitis, upon subsidence of temperature there is a concomitant amelioration of local symptoms of pain and discomfort. It cannot then be acknowledged, from the facts presented for the surgical approach, that the operative procedure contributed a great deal of benefit toward the treatment of mumps orchitis.

Nixon and Lewis were able to follow up 27 of their 68 patients for periods of three months to two years following surgery. They found definite atrophy of the testis of one patient. In the other 26 cases there was testicular softening but no atrophy. If these 27 cases are truly representative of the 66, then 100 per cent of cases showed a loss of turgor of the involved testicle. In our own series of 78 involved testes, upon discharge only 44.9 per cent (35 cases) showed loss of turgor, and 55.1 per cent (43 cases) were normal. In a previous study (1945) of 49 cases of orchitis examined on the average six years after the occurrence of the orchitis, 55 per cent (27 testes) showed loss of turgor and atrophy, while 45 per cent (22 testes) were normal. It would seem, then, that after an operative procedure loss of turgor (which we believe represents a stage of atrophy) is more frequent than in the conservatively treated patient. It may take longer than three months to two years for maximum atrophy to develop, since in our present series of 78 patients, on discharge only four cases showed any atrophy and 31 loss of turgor without diminution in size; while in the 49 cases studied on the average of six years after disease, 22 cases (45 per cent) showed variable diminution in size of the involved gonads.

One cannot help making some remarks concerning sterility and mumps. It is an almost universal belief among laymen that mumps orchitis is a common cause of sterility. This concept is not confined to the laity. One recent text holds that mumps is a common cause of sterility and hypogonadism.⁷² In the current literature, an inference may be found that mumps orchitis may cause impotence.⁷¹

In 1920, Wesselhoeft⁷³ stated that mumps may cause sterility in the male, but he was able to collect only two cases from the literature where sterility was definitely thought to be due to mumps. In one case the double testicular atrophy was not stated to be complete but was associated with induration of the epididymis. In the other case, both testes were said to be completely atrophic. Wesselhoeft was of the opinion that sterility in mumps

was rare. He believed that destruction of the epididymis or the vas deferens, and atrophy of the prostate and Cowper's glands, would place greater difficulties in the way of reproduction than partial testicular atrophy. He stated that destruction of these structures was much less common in mumps than in gonorrhea. In 1927, Bénard⁷⁴ wrote a paper which was entitled "Sterility Following Adult Mumps Is a Myth." He pointed out, quite naturally, that sterility is no problem in unilateral orchitis. He placed the incidence of bilateral orchitis in adult mumps at 2 per cent. (Our own series showed an incidence of 5.4 per cent.) He stated, further, that bilateral orchitis is not of importance if it is not followed by atrophy. He found that only 50 per cent of cases of orchitis are followed by atrophy. (This is in agreement with other authors as well as our own observations.) Of the remainder who showed any atrophy, usually only partial atrophy occurred. There was no complete atrophy in any of his cases. He found none less than half the size of normal. (We found one-third of our cases approximately one-third the size of normal,¹ but none any smaller than this.) Bénard's most interesting contribution was a follow-up and study of the seminal fluid of seven cases of orchitis of which five were bilateral. He observed that the number and viability of spermatozoa were absolutely normal. More studies of this nature would be very valuable, particularly since so much more has been learned regarding the examination of spermatozoa since 1927.

In a recent study on fertility of the male in barren marriages, Michelson and Michelson⁷⁵ surveyed 519 men with impaired fertility (determined by an analysis of the semen). In 76 per cent of these, no cause could be determined. In the 24 per cent (126 cases) of known etiology, 13 were said to be due to bilateral mumps orchitis and seven were said to be due to unilateral mumps orchitis. In the latter, the authors postulated that there was probably a bilateral orchitis with apparently such slight involvement of one gonad as to escape detection. It is difficult to escape an alternate possibility, namely, that of the 20 cases of infertility ascribed to mumps orchitis, some or all may have been due to unknown factors which were responsible for the impaired fertility noted in the 76 per cent of cases, and not really due to the mumps orchitis.

Bénard concluded that bilateral mumps leading to impotence is a fiction. Wesselhoeft never found mention of a eunuch as a result of mumps. He explained this by the infrequency of orchitis in childhood. It must also be mentioned that, since complete atrophy of the testes in bilateral adult mumps must be a very great rarity, adult castration as a result of mumps could hardly be expected to be observed with frequency.

DISCUSSION

Although there have been many observations on epididymitis in association with mumps orchitis, this information has not been reflected ade-

quately or accurately in many texts of medicine, urology and contagious diseases. Epididymitis must be considered as a part of the complication of orchitis. The vast majority of studies that have been made with the view in mind of ascertaining the existence of epididymitis have shown that it is common. Yet there are a small number of instances where the involvement seems to be minimal. By far the greater number (85 per cent in our series) show that the epididymis is involved to a considerable degree.

Epididymitis has been noted at times to precede the orchitis by days. Most often it appears to occur at the same time. Some observers have expressed the opinion that epididymitis always precedes testicular involvement. Occasional cases have been reported in which the epididymis alone was involved.

The term epididymo-orchitis probably gives the best description of the extent of anatomic involvement. The funiculus may likewise be affected. The symptomatology cannot be broken down into the part due to epididymal and that due to testicular implication. It must be considered to be due to both.

Epididymo-orchitis may occur before, coincidental with, or after parotitis. It may be present in systemic mumps without salivary gland involvement. The diagnosis is relatively simple when parotid, submaxillary or sublingual gland swelling becomes manifest. When these are absent, aids in diagnosis include: (1) history of contact with mumps; (2) signs of meningitis; (3) serum amylase elevation if parotitis was present but was missed clinically; (4) complement fixation test, and (5) skin test for dermal hypersensitivity.

The clinical manifestations of epididymo-orchitis are reflected by constitutional symptoms and local symptoms. Fever is usually present but may be minimal when the gonadal involvement is slight. Chills, headache, nausea and vomiting may occur. Fever lasted no more than five days in 83.8 per cent of our cases. In 22.5 per cent it lasted three days or less. In our particular series, none showed fever after seven days. In another series, one case was encountered in which the temperature was elevated for nine days. In bilateral epididymo-orchitis, fever may last longer than usual if the testes are involved consecutively and not simultaneously. Fever subsided by crisis in approximately 50 per cent of cases. With the subsidence of fever there was an amelioration of local as well as of general symptoms. The temperature varied from 99° to 106° F. orally and the mode was around 103° F. The more usual range is 101° to 106° F. Locally, pain, swelling, and tenderness of the gonad were present. The differentiation of epididymal from testicular swelling can be made out quite readily, except when there is considerable gonadal swelling. Under such circumstances, palpation daily will differentiate them, because the rate of subsidence of testicular swelling differs from the epididymal swelling. Approximately 45 per cent of all involved testes in this series (see table 9) showed loss of turgor on discharge. Only 5.1 per cent showed atrophy on discharge. In

another series, studied on the average of six years after the original orchitis, 55 per cent showed atrophy as well as loss of turgor. One must then infer that, since shortly after orchitis only few testes show notable atrophy as well as loss of turgor, the process of atrophy is progressive and takes place over an extended period of time.

Hypogonadism and impotence as a result of testicular destruction have not been demonstrated. Sterility as a consequence of mumps epididymo-orchitis is probably infrequent. In those instances where sterility may be shown to be due to the gonadal complication, more attention should be given to the state of the epididymis to determine whether it is the offending factor rather than the involved testicle. In our study, 19 of 74 involved gonads showed residual epididymal thickening upon discharge from the hospital (see table 2). More studies of the seminal fluid, including serial studies over long periods of time, are necessary to determine the exact extent to which sterility may be ascribed to mumps.

Work has been done in developing a vaccine which will induce immunity against mumps. Successful development of this vaccine will make mass prophylaxis possible. When mumps has appeared clinically, intramuscular injection of 20 c.c. of gamma globulin prepared from convalescent serum has been shown to reduce considerably the incidence of epididymo-orchitis. Once the inflammatory process has affected the gonad, treatment is purely symptomatic. Pooled plasma is useless in therapy. The surgical treatment of mumps orchitis does not appear to have any unequivocal advantage, in spite of the claims made for it.

Therapeutic research in the treatment of mumps epididymo-orchitis must be carefully controlled. Cognizance of the natural history of the complication is imperative. The factors to be taken into consideration are: (1) short duration of fever; (2) fall of temperature by crisis in half the cases; (3) loss of turgor or of the testicle in 45 per cent of cases, and (4) progressive atrophy which takes place over an extended period of time.

SUMMARY

1. Epididymitis was found to be present in association with 85 per cent of cases of mumps orchitis. In the remaining 15 per cent, it was difficult to exclude the presence of an inflammatory process.
2. Clinical studies on epididymo-orchitis have been described.
3. Reference has been made to problems of diagnosis, prophylaxis, therapy, and sequelae of epididymo-orchitis.

BIBLIOGRAPHY

1. Candel, S., Wheelock, M. C., and Grimaldi, G. J.: Mumps orchitis, U. S. Naval M. Bull. 45: 97-106, 1945.
2. Waddelow, J. J.: Primary epididymitis in mumps, Brit. M. J. 1: 1480, 1909.
3. Feiling, A.: Mumps—a critical review, Quart. J. Med. 8: 255-276, 1914-15.

4. Madamet (2 cases); and Morel-Lavallée in 1848 (1 case) cited by Catrin¹¹; Chauvin (2 cases) cited by Feiling.³
5. Smith, G. C.: Two cases of orchitis due to mumps treated by operation, Boston M. and S. J. 167: 323-325, 1912.
6. Sorel, M.: Contribution à la thermométrie clinique de la fièvre dans l'orchite symptomatique des oreillons, Rev. mens. de méd. et de chir. 1: 280-288, 1877.
7. Rambar, A. C.: Pooled plasma treatment of mumps orchitis, U. S. Naval M. Bull. 42: 871-873, 1944.
8. Rambar, A. C.: Use of convalescent serum in the treatment and prophylaxis of orchitis, Am. J. Dis. Child. 71: 1-13, 1946.
9. Smith, R. G.: Plasma treatment of orchitis: 5 cases, U. S. Naval M. Bull. 44: 159-160, 1945.
10. Laveran, A.: Traité des maladies et des épidémies des armées, 1875, G. Masson, Paris, pp. 550-559.
11. Catrin, M.: Orchite ourlienne, Bull. et mém. Soc. méd. d. hôp. de Paris 11: 108, 1894.
12. Radin, M. J.: The epidemic of mumps at Camp Wheeler, Oct. 1917-March 1918, Arch. Int. Med. 22: 354-369, 1918.
13. Rabinowitz, M. A., and Seligman, B.: Primary mumps orchitis without parotitis, M. J. and Rec. 130: 215-216, 1929.
14. Harris, W., and Bethell, H.: Meningo-encephalitis and orchitis as only symptoms of mumps, Lancet 2: 422, 1938.
15. Derrmon, H., and Le Hew, W.: Mumps epidemic in a small task force, Am. J. M. Sc. 208: 240-247, 1944.
16. Candel, S., Wheelock, M. J., Turk, J. P., Jr., and Smoot, J. L.: Mumps meningitis, U. S. Naval M. Bull. 42: 861-870, 1944.
17. Thomson-Walker, J.: Diseases of the genito-urinary organs, Edited by Kenneth Walker, 1936, William Wood & Co., Baltimore, p. 858.
18. Goodall and Washbourn: Infectious diseases by E. W. Goodall, 3rd Ed., 1928, H. K. Lewis & Co., London, pp. 450-451.
19. Boyd, W.: Surgical pathology, 6th Ed., 1947, W. B. Saunders Co., Philadelphia and London, p. 444.
20. Cecil, R. L.: Textbook of medicine, 7th Ed., 1947, W. B. Saunders Co., Philadelphia, p. 46.
21. Eisendrath, D. N., and Rolnick, H. C.: Urology, 1938, J. B. Lippincott Co., Philadelphia, p. 395.
22. Le Comte, R. M.: Manual of urology, 3rd Ed., 1944, Williams & Wilkins, Baltimore, p. 271.
23. Christian, H. A.: Oxford medicine, mumps, infectious diseases, Oxford University Press, New York, Vol. V, Part ii, p. 497.
24. Abt, I. A.: Pediatrics; mumps, 1925, W. B. Saunders Co., Philadelphia, p. 284.
25. Rolleston, J. D., and Ronaldson, G. W.: Acute infectious diseases, 3rd Ed., 1940, C. V. Mosby Co., St. Louis.
26. Conybeare, J. J.: Textbook of medicine, 6th Ed., 1942, William Wood & Co., Baltimore, p. 37.
27. Meakins, J. C.: The practice of medicine, 4th Ed., 1944, C. V. Mosby Co., St. Louis, p. 97.
28. Kers: Infectious diseases—a practical textbook, Revised by Claude Rundle and Humphrey Milford, 1929, Oxford University Press, London, p. 517.
29. Campbell, M. F.: Pediatric urology, 1937, The Macmillan Co., N. Y., Vol. 2, p. 113.
30. Herman, L.: The practice of urology, 1938, W. B. Saunders Co., Philadelphia, pp. 663-664.

31. Stimson, P. M.: A manual of the common contagious diseases, 1947, Lea and Febiger, Philadelphia, p. 255.
32. Musser, J. H.: Internal medicine—its theory and practice, 4th Ed., 1945, Lea and Febiger, Philadelphia, p. 393.
33. Osler's Principles and practice of medicine by Henry A. Christian, 16th Ed., 1947, D. Appleton-Century Co., New York and London, p. 352.
34. Yater, W. M.: Fundamentals of internal medicine, 2nd Ed., 1944, D. Appleton-Century Co., N. Y., p. 729.
35. Fox, M. J.: Mumps, Practice of medicine, 1947, Edited by Tice, F., W. F. Prior, Hagerstown, Md., Vol. 3, p. 318.
36. Top, F. H.: Handbook of communicable diseases, 2nd Ed., 1947, C. V. Mosby Co., St. Louis, p. 512.
37. Harries, E. H. R., and Mitman, M.: Clinical practice in infectious diseases, 1940, Williams and Wilkins Co., Baltimore, 228-229.
38. Savill's System of clinical medicine, 12th Ed., 1944, Williams and Wilkins Co., Baltimore, pp. 601-602.
39. Hinman, F.: Principles and practice of urology, 1935, W. B. Saunders Co., Philadelphia, p. 787.
40. Keyes, E. L., and Ferguson, R. S.: Urology, 1936, D. Appleton-Century Co., N. Y., pp. 474 and 482.
41. Helmoltz, H. F., Amberg, S., and Haynes, R. S.: Diseases of the genito-urinary system in infancy and childhood, 1930, D. Appleton & Co., New York, pp. 216 and 219.
42. McCrea, L. E.: Clinical urology, 1946, F. A. Davis Co., Philadelphia, p. 134.
43. Cabot, H.: Modern urology, 3d Ed., 1936, Lea and Febiger, Philadelphia, Vol. 1, p. 483.
44. Ockerblad, N. F., and Carlson, H. E.: Urology in general practice, 2nd Ed., 1947, The Year Book Publishers, Chicago, pp. 291 and 294.
45. Pelouze, P. S.: Office urology, 1940, W. B. Saunders Co., Philadelphia, pp. 414, 428-429.
46. Hyman, H. T.: An integrated practice of medicine, 1946, W. B. Saunders Co., Philadelphia, Vol. 3, p. 2461.
47. Sterling, C.: The cyclopedia of medicine, surgery and specialties, George Morris Piersol, Editor, 1946, F. A. Davis Co., Vol. 14, 992-999.
48. Roche, A. E.: Urology in general practice, 1935, H. K. Lewis & Co., Ltd., London, pp. 303-308.
49. Trousseau, A.: Lectures on clinical medicine, 1869, The New Sydenham Society, London, Vol. II, pp. 277-281.
50. Boutelle, J. T.: Cases of mumps complicated with epididymitis, Boston M. and S. J. 94: 384-386, 1876.
51. Phillips, S.: Note on a case of mumps in which attacks of epididymitis occurred on each side in turn, each attack being accompanied by symptoms profoundly involving the nervous system, Lancet 1: 23, 1911.
52. Wesselhoeft, C.: Orchitis in mumps, Boston M. and S. J. 183: 458-461, 1920.
53. Zax, E.: Mumps epididymo-orchitis without involvement of the salivary glands, with a case report, Urol. and Cutan. Rev. 41: 624, 1937.
54. Zax, E.: Mumps epididymo-orchitis without salivary gland involvement: report of a second case, Urol. and Cutan. Rev. 47: 173, 1943.
55. Hammersley, A.: Observations on cyanache parotidoea as it occurred in the N. Y. State Prison during winters of 1821 and 1822, N. Y. Med. Repository, July, 1822, 416-417. (Quoted by Wesselhoeft.⁵²)
56. Phares, D. L.: Mumps metastases, Trans. Miss. M. A., Jackson, Mississippi 16: 114-115, 1883.
57. Finkelstein, H.: Meningo-encephalitis in mumps, J. A. M. A. 3: 17-19, 1938.
58. Applebaum, I. L.: Serum amylase in mumps, Ann. Int. Med. 21: 35-43, 1944.

59. Candel, S., and Wheelock, M. C.: Serum amylase and serum lipase in mumps, *Ann. Int. Med.* **25**: 88-96, 1946.
60. Enders, J. F., Cohen, S., and Kane, L. W.: Immunity in mumps, *J. Exper. Med.* **81**: 119-135, 1945.
61. Stokes, J. J., Enders, J. F., Maris, E. P., and Kane, L. W.: Immunity in mumps—experiments on the vaccination of human beings with formolized mumps virus, *J. Exper. Med.* **84**: 407-428, 1946.
62. De Lavergne, V., and Florentine, P.: Convalescents' serum in prevention of orchitis in mumps, *Bull. Acad. de méd., Paris* **93**: 362, 1925; *Abstr. J. A. M. A.* **84**: 1701, 1925.
63. Teissier: Prophylactic value of convalescents' serum in mumps, *Bull. Acad. de méd., Paris* **93**: 369, 1925; *Abstr. J. A. M. A.* **84**: 1701, 1925.
64. Hinckley, R. G.: Therapeutic use of convalescent serum in mumps, *Minnesota Med.* **20**: 227, 1937.
65. Bailey, W. H., and Haerem, A. T.: Some observations on efficacy of convalescent mumps serum, *Mil. Surgeon* **90**: 134-139, 1942.
66. Enders, J. F.: Chemical, clinical and immunological studies on the products of human plasma fractionation. X. The concentration of certain antibodies in globulin fractions derived from human blood plasma, *J. Clin. Investigation* **23**: 510-531, 1944.
67. Gellis, S. S., McGuiness, A. C., and Peters, M.: A study of the prevention of mumps orchitis by gamma-globulin, *Am. J. M. Sc.* **210**: 661-664, 1945.
68. Candel, S.: Immune serum globulin (gamma-globulin) in the prophylaxis of mumps orchitis, *Mil. Surgeon* **99**: 199-202, 1946.
69. Enders, J. F.: Quoted by Gellis, S. S.⁶⁷
70. Savran, J.: Diethylstilbestrol in the prevention of orchitis following mumps, *Rhode Island M. J.* **29**: 662, 1946.
71. Nixon, N., and Lewis, D. B.: Mumps orchitis, surgical treatment, *J. Urol.* **56**: 554-560, 1946.
72. Hyman, H. T.: *An integrated practice of medicine*, 1946, W. B. Saunders Co., Philadelphia, Vol. 3, p. 2464.
73. Wesselhoeft, C.: Orchitis in mumps, *Boston M. and S. J.* **183**: 520-524, 1920.
74. Bénard, R.: La sterileté, consécutive aux oreillons de l'adulte est un mythe, *Médecine* **9**: 184-189, 1927.
75. Michelson, L., and Michelson, R.: Fertility studies of the male in barren marriages, *J. A. M. A.* **134**: 941-944, 1947.

OBSERVATIONS ON PORTAL CIRRHOSIS WITH ASCITES *

By WILLIAM E. RICKETTS, M.D., Ph.D., *Chicago, Illinois*

THE pathogenesis, as well as the treatment, of edema and ascites in portal cirrhosis has been a subject of utmost interest and continuous investigation. Attention has been directed to the rôle of proteins and the colloid osmotic pressure of the plasma,^{1, 2, 3, 4, 5, 6, 7, 8, 9} to disturbances in electrolyte excretion^{10, 11, 12} and to urine output.⁶ Previous studies have shown that the plasma albumin was consistently within the normal range in patients with latent, asymptomatic cirrhosis,^{13, 14} whereas it was consistently reduced in patients with portal cirrhosis accompanied by severe jaundice and ascites. Clinical improvement following medical management was associated with a gradual return of the albumin and total plasma proteins to within normal range and by a simultaneous disappearance of ascites.¹⁵

The purpose of the present study is (a) to analyze the relationship of the plasma proteins in untreated cases of portal cirrhosis, and (b) to evaluate the effect of medical management on the concentration of plasma proteins, on ascites, and on the course of the disease.

RELATIONSHIP OF PLASMA PROTEINS TO ASCITES IN UNTREATED CASES OF PORTAL CIRRHOSIS

Fifty patients with untreated portal cirrhosis without cardiorenal disease were studied. Duplicate measurements were made of the total plasma proteins and albumin and globulin fractions¹⁶ at the beginning of the period of observation. Twenty healthy persons, varying in age from 16 to 32 years, served as controls. In the absence of plasma volume determinations, the quantity of circulating proteins cannot be stated.

The values for total proteins, albumin and globulin in patients with and without ascites are compared in figure 1. The most significant abnormalities are found in the levels of plasma albumin. The values for total proteins, globulin and albumin of patients with cirrhosis but without ascites show considerable overlapping with those found in normal persons. Plasma albumin levels in patients with cirrhosis and ascites were consistently below 3 gm. per cent, while those of normal persons and patients with cirrhosis but without ascites exceeded this figure. This decrease of albumin was usually attributed to one or more factors: an insufficient intake of food, inadequate production and utilization of proteins by the diseased liver, loss of protein from repeated paracenteses, massive hemorrhage, diarrhea or in-

* Received for publication May 17, 1950.

From the Frank Billings Clinic, the Department of Medicine, University of Chicago, Chicago, Illinois.

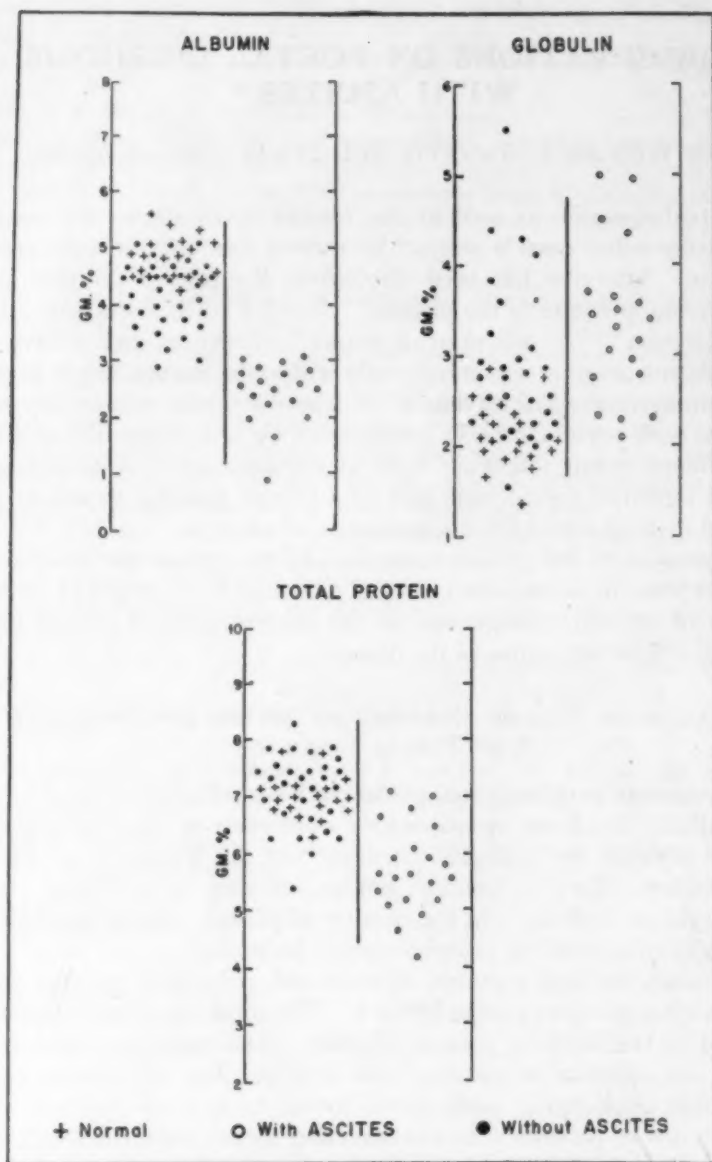


FIG. 1. Plasma proteins in normal individuals and in portal cirrhosis with and without ascites.

fection. The values for globulin did not exceed 2.8 gm. per cent in the 20 normal subjects, whereas higher values were frequently obtained in patients with portal cirrhosis. The rise in globulin on the average was higher in patients with ascites than in those without ascites (table 1).

TABLE I

	No. Cases	Plasma Proteins Gm. per cent					
		Total Protein		Albumin		Globulin	
		Mean	S.D.*	Mean	S.D.*	Mean	S.D.*
Normals	20	7.02	0.31	4.81	0.34	2.18	0.35
Portal Cirrhosis without Ascites	30	7.20	0.37	4.19	0.15	3.04	1.03
Portal Cirrhosis with Ascites	20	5.70	0.37	2.39	0.24	3.32	0.60

* Standard deviation.

Other investigators, by various protein-precipitating methods ^{4, 5, 6, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32} and by electrophoresis, ^{32, 33, 34, 35} have noted decreased albumin and increased globulin in portal cirrhosis. In a previous electrophoretic study, ³³ a marked decrease in albumin was found in five cases with ascites, in contrast to patients without ascites, in asymptomatic cases, or in cases which had recovered from ascites after medical treatment. ³⁶

The relation of plasma albumin and plasma globulin values to the presence of ascites is illustrated in figure 2. It is apparent that the increased globulin may occasionally be of sufficient magnitude to raise the colloid osmotic pressure, and thereby to lessen or even to prevent the development of ascites and edema.

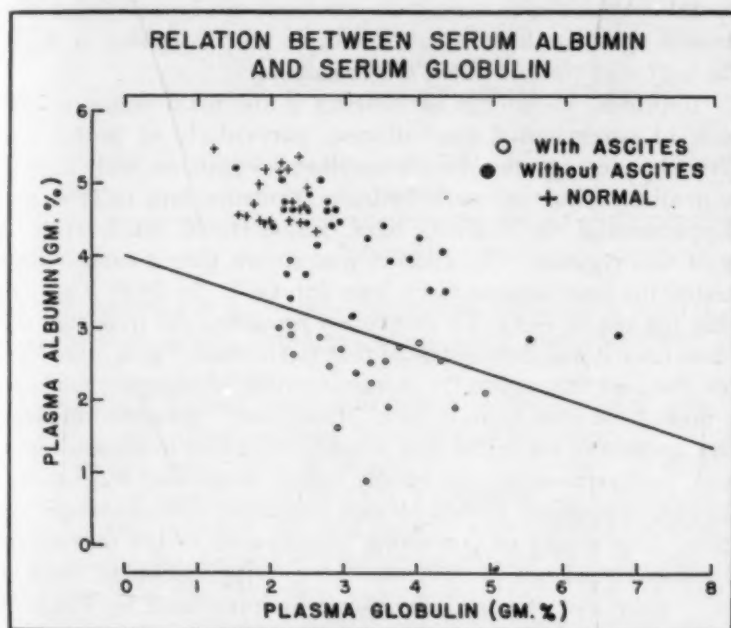


FIG. 2.

MEDICAL MANAGEMENT OF PORTAL CIRRHOSIS WITH ASCITES

The medical management of portal cirrhosis with ascites is one of the most complex problems encountered in medicine and one in which great advances have taken place in recent years. At the present time, the principles of therapy appear to be clear-cut: to avoid further injury to the liver by toxins such as alcohol; to promote regeneration of the hepatic parenchyma; to improve the general nutrition of the patient, and to correct the tendency to retention of water and salt in the body. The first three principles apply to all patients with liver disease, and the last only to cases with edema and ascites.

Chronic alcoholism is the most frequent cause of portal cirrhosis; in the experience of this institution, 75 per cent of the cases are so caused.¹⁴ One of the most important points in the management of these patients, therefore, is abstinence from alcohol. This may be a difficult problem and one that demands careful medical handling; however, abstinence from alcohol was achieved in the great majority of the patients treated. A few cases required special psychiatric treatment.

In the medical management of portal cirrhosis with ascites, the following measures will be considered separately: bed rest, diet, vitamins, lipotropic substances, restriction of sodium intake, parenteral protein, paracentesis and diuretics.

Bed Rest: Prolonged and complete bed rest is advisable for all patients having portal cirrhosis with ascites or jaundice. Bed rest lowers the metabolic demands upon the liver. In most cases hospitalization is imperative, as it is the only way to control the water balance.

Diet: Improved knowledge of dietetics is the main factor in changing the outlook of parenchymal liver disease, particularly of portal cirrhosis. Until a few decades ago the diets prescribed to patients with liver disease were low in all constituents—carbohydrates, proteins, fats, calories and vitamins. Experimental observations have demonstrated conclusively the inadequacy of this regimen. In 1920 it was shown that a carbohydrate-rich diet protected the liver against toxic liver injury.³⁷ In 1939 it was demonstrated that the use of diets rich in protein protected the liver against toxic injury,³⁸ and later it was demonstrated that methionine³⁹ and other lipotropic substances also had this action.⁴⁰ Administration of vitamins was also suggested to protect the liver from injury. Hoagland⁴¹ presented evidence that a moderate amount of fat in the diet was not injurious to patients with liver disease and, furthermore, was extremely helpful in making diets more palatable. The rôle of proteins, carbohydrates, lipotropic substances and vitamins in preventing liver injury or promoting regeneration of the parenchyma has been proved and need not be reviewed here. Application of these dietary principles to treatment of portal cirrhosis was introduced by Patek and his associates⁴² with excellent results, and confirmed by others.

A diet containing 120 gm. of protein, 350 to 400 gm. of carbohydrate, and 3,000 to 3,500 calories, supplemented by 6 gm. of choline chloride, was found to improve nutrition, increase the plasma proteins and eliminate edema and ascites. Changes in the plasma protein sometimes required several months to become evident. This is illustrated in seven patients in whom no parenteral protein therapy or repeated paracenteses were done (figure 3). However, an adequate intake of protein and food in many cases is not possible because of anorexia; thus adequate nutrition of patients with severe liver failure may be extremely difficult. Often the anorexia is only transitory and disappears with the subsidence of symptoms of parenchymal failure. Increase of appetite may be brought about after infusions of plasma albumin.

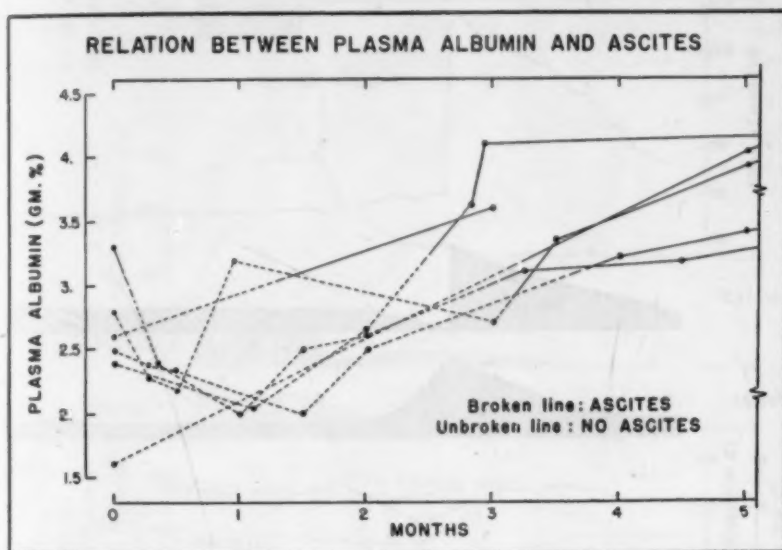


FIG. 3.

However, the method of preference for protein repletion is enteral. Parenteral therapy is especially indicated when acute loss of protein or shock has occurred.

Fluid and Salt Intake: Administration of an adequate diet does not bring about prompt disappearance of ascites in the majority of cases, for several months are required to achieve protein repletion. In these patients it is absolutely necessary to control the balance of body fluids which have a marked tendency to retain salt and must be considerably reduced. A 500 mg. daily sodium intake will prevent weight gain due to fluid retention. It is surprising that this extremely important measure has not been advised until recently.¹⁰ Restriction of salt intake while body proteins are restored through adequate nutrition permits control of the tendency to fluid retention

without the use of repeated paracenteses and diuretics. A diet considerably restricted in sodium is well tolerated by most patients.

The tendency to retention of sodium in portal cirrhosis has been reported only recently.¹¹ It appears to depend on increased re-absorption of sodium

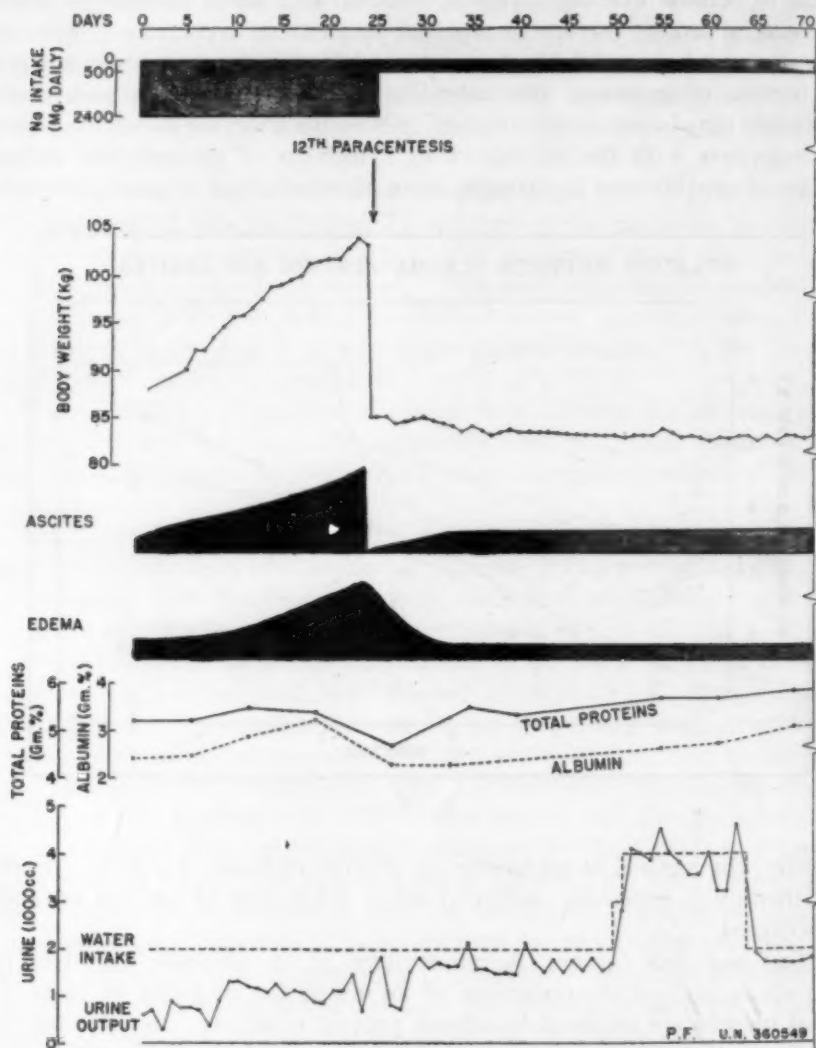


FIG. 4. Control of weight, edema and ascites with a 500 mg. sodium intake daily.

in the tubules of the kidney, and is not due to a defect in glomerular filtration. Preliminary unpublished studies by us¹² have demonstrated that poor elimination of sodium in the urine occurs in portal cirrhosis with ascites and poor nutrition, but does not occur in portal cirrhosis without ascites

and with normal proteins, or in cases which previously had had ascites but had recovered completely for two years or longer. Cases of portal cirrhosis without edema or ascites need no sodium restriction.

The effect of restriction of sodium in controlling the tendency to fluid retention in cases with ascites is well illustrated in figures 4, 5 and 6. Occasionally, the simple restriction of sodium brings about a rapid disappearance of ascites without the use of diuretics, as is illustrated in figure 9. In most cases, however, this tendency to retain fluids and salt disappears only

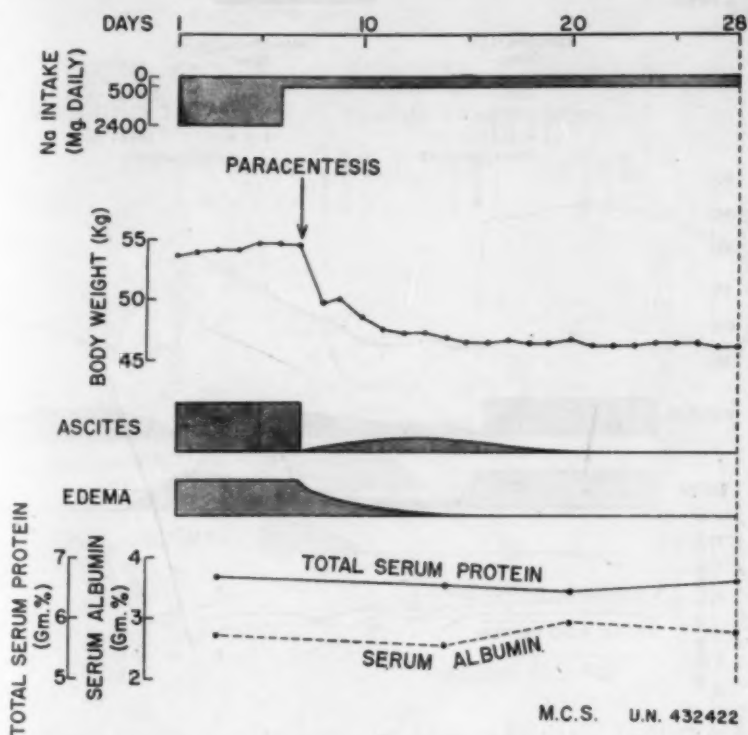


FIG. 5. Disappearance of edema and ascites in three weeks, without use of diuretics, with a 500 mg. Na intake daily.

after several months of medical management. In figure 6 it is clearly seen that when the intake of sodium increased from 500 mg. to 2,400 mg. daily in a patient with marked depletion of proteins and extremely poor excretion of sodium by the kidney, a progressive gain in weight took place which could not be controlled by the administration of mercurial diuretics. Edema and ascites increased and necessitated another paracentesis.

Parenteral Protein Therapy: The effects of parenteral protein therapy vary considerably, depending on the type of protein given, the daily intake

of salt, and the responsiveness of the individual patient, a factor not readily predictable. In figure 7, without restriction of dietary sodium nine infusions of 1,000 c.c. of plasma brought about a disappearance of edema and ascites with a marked rise in the plasma proteins. The same amount of plasma given to another patient with impaired salt excretion was fol-

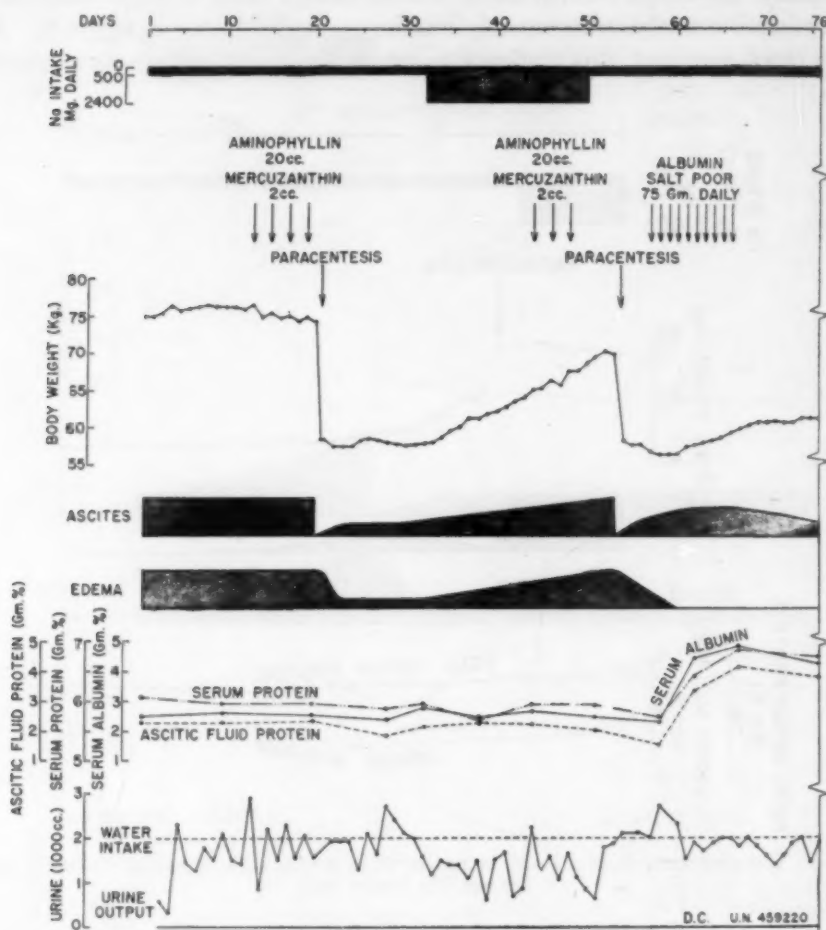


FIG. 6. Uncontrolled gain in weight, edema and ascites, with 2,400 mg. Na intake daily despite use of mercurial diuretics. Ready control under a 500 mg. Na intake daily.

lowed by a gain in weight and an increase in ascites and edema. This was due to the retention of salt contained in the infusions (figure 8).

The effects of salt-poor albumin infusions have been described by several authors.^{43, 44, 45, 46, 47, 48, 49, 50} In our experience results vary, depending on the salt intake and on the individual response. This is illustrated in figures 6, 8 and 9. The ascites may disappear very rapidly when the daily sodium

intake is restricted to 500 mg. (figures 8 and 9), or no remarkable immediate change may occur (figure 6). Salt-poor albumin, when given with a daily sodium intake of 2,400 mg. by mouth to a patient unable to eliminate sodium adequately, did not prevent a gain in weight due to water retention (figure 8). In circulatory collapse with marked drop in blood pressure and decrease in filtration pressure, the administration of plasma or salt-poor albumin may be a life-saving procedure.

Water-soluble extract of liver has been given intravenously by Hoagland, et al.⁴¹ to patients with hepatic insufficiency. I have had no personal experience with this type of therapy.

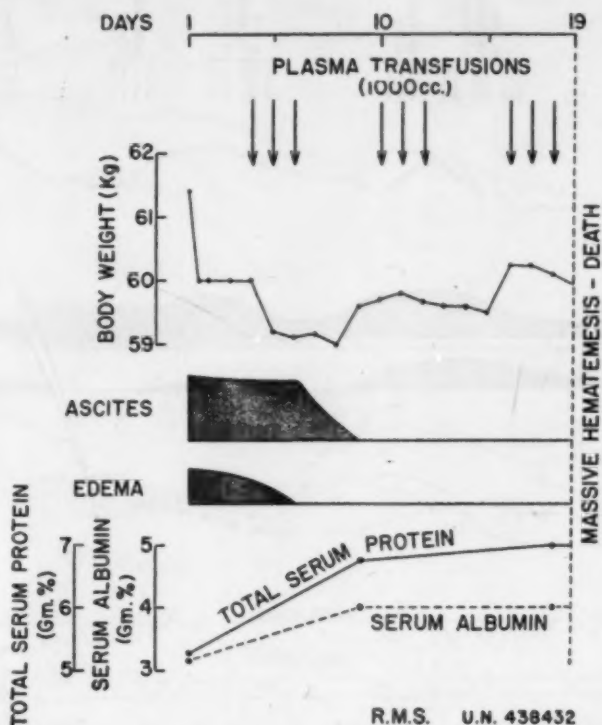


Fig. 7. Rapid disappearance of edema and ascites without appreciable loss of weight following infusions of plasma.

Paracentesis, Diuretics: Paracentesis is often imperative in patients with great discomfort from marked ascites. This measure affords considerable relief and, if followed by restriction of sodium to 500 mg. daily, controls the retention of water (figures 4, 5 and 6). Following paracentesis, ascites re-accumulates at the expense of edema fluid, while total body weight does not change. If the paracentesis is followed by excessive sodium intake, edema and ascitic fluid will again accumulate, and in a matter of a few weeks the patient will require another paracentesis. The end result of this vicious

circle of repeated paracenteses without control of dietary sodium is further deproteinization, since large amounts of protein are lost with the withdrawal of ascitic fluid.

Oliguria may occur in portal cirrhosis from various mechanisms. Oliguria due to circulatory failure is today rather uncommon in portal cirrhosis with ascites. It was more prevalent in the era in which paracentesis was

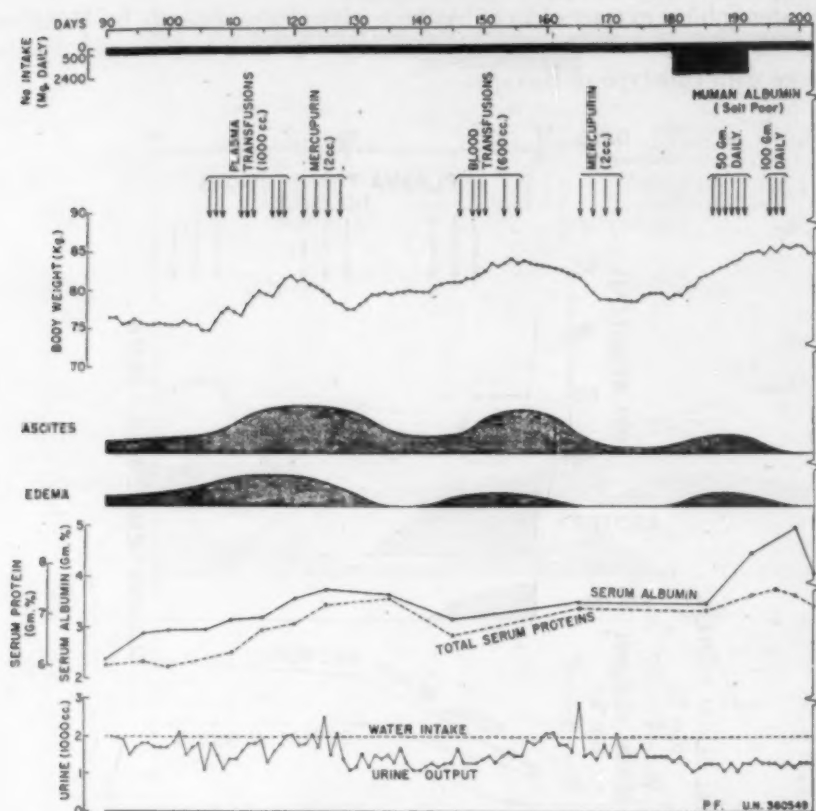


FIG. 8. Increase of weight, edema and ascites following plasma and blood transfusions; same phenomena after infusions of salt-poor albumin when patient was maintained in 2,400 mg. Na intake daily.

done routinely, when severe shock-like episodes were not uncommon after the withdrawal of ascitic fluid. In portal cirrhosis with ascites, the blood pressure and the urea clearance are usually within normal limits.

Ralli et al.⁶ studied the presence of an antidiuretic factor in varied conditions. They found that the urine of patients with portal cirrhosis and ascites had a marked antidiuretic effect in experimental rat assays. The magnitude of the effect seemed to parallel the degree of the ascites. This

effect was very slight in normal individuals and in patients with portal cirrhosis without ascites. Hoagland⁴¹ assumed that the antidiuretic factor was a hormone, probably from the posterior pituitary gland, but no proof has been given of its existence. In my experience, salt itself appeared to

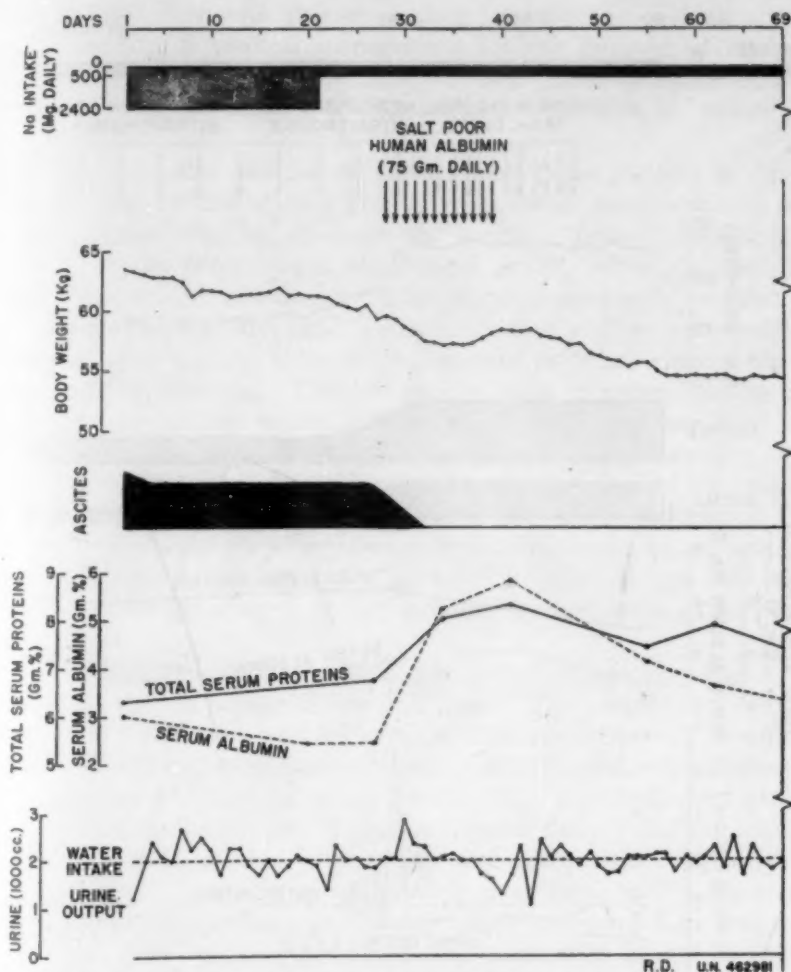


FIG. 9. Dramatic disappearance of edema and ascites after infusion of 300 gm. of salt-poor albumin.

have a considerable antidiuretic effect, as is illustrated in figures 4 and 6. The restriction of salt to 500 mg. was followed by an immediate diuresis. The administration of 2,400 mg. of salt reduced urine output one-third or more. When sodium is restricted to 500 mg. daily, increase in water intake is followed by a corresponding increase of urine output.

The use of diuretics, particularly mercurial diuretics, in the treatment of portal cirrhosis with ascites dates from ancient times. For many years it has been known⁶¹ that there are limitations in its use, as illustrated in figures 6, 8, 9 and 10. Mercurial diuretics do not control progressive gain

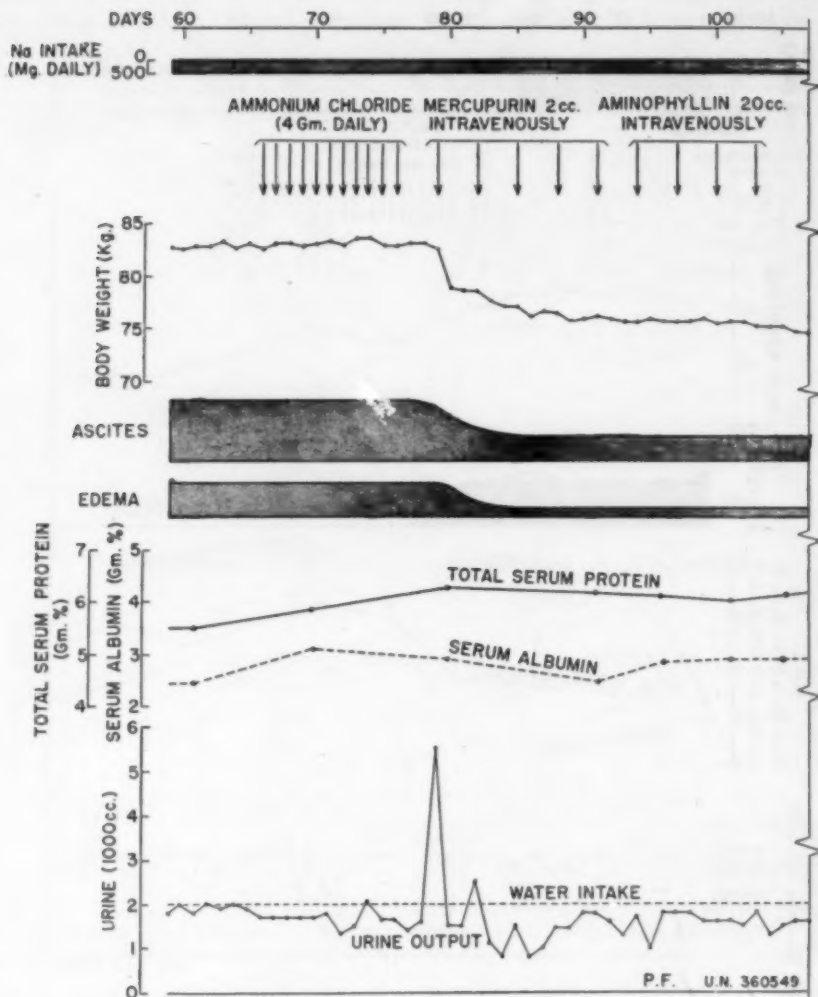


FIG. 10. Inconstant effects of diuretics in patient with portal cirrhosis with ascites and edema.

in weight on a 2,400 mg. daily sodium intake. There is very little need for diuretics if sodium is restricted to 500 mg. or less daily. However, diuretics may be quite useful if this restriction is not entirely adequate.

Results of Medical Management: The results of medical management in cases of portal cirrhosis depend on innumerable factors. Except for a few

additional measures during the period of edema and ascites, the medical management is not very different in cases with and without ascites. Ascites and edema may be precipitated by several causes. Among these are gastrointestinal bleeding, infections (e.g., bronchopneumonia, gastroenteritis), diarrhea of undetermined cause, laparotomy, or severe alcoholic intoxication lasting several days with little or no food intake.

The results of medical management for the purpose of analysis are divided into two groups: the first, 14 cases with jaundice and severe hepatic failure; the second, 13 cases without jaundice or severe hepatic failure.

Marked Jaundice and Severe Liver Failure: The patients in this group were admitted to the hospital greatly confused or semicomatose, severely ill, with marked oliguria, anasarca and ascites. Tests of hepatic function disclosed severe parenchymal impairment in all, while the morphologic studies of the liver obtained by liver biopsy consistently revealed severe parenchymal degenerative and necrotic changes. The treatment of the "hepatitis" in this group is the most important problem, whereas the ascites is of secondary interest. The tendency to fluid retention may be readily controlled by a sodium intake of 500 mg. or less. As there is no specific treatment for this "hepatitis," supportive therapeutic measures are of prime importance. Salt-poor albumin or plasma infusions may be life-saving procedures, particularly in circulatory collapse and marked oliguria. One or two liters of glucose given intravenously may maintain an adequate water intake for patients unable to take fluids by mouth. In general, infusions of saline should be avoided as they produce further anasarca and increase in ascites.

The immediate mortality of this group of cases was very high. Of 14 patients, six died in hepatic failure and coma. The situation was extremely desperate in others but was followed by dramatic recovery. Feedings by mouth in these cases were started promptly and progressively increased until the patients were able to eat a high protein, high carbohydrate, high caloric diet with an additional 6 gm. of choline chloride daily. Sodium intake was restricted for a short time after ascites and edema had completely disappeared. Hospitalization was continued in most cases until the patients no longer had ascites or edema, and the jaundice had completely disappeared. In the few follow-up cases, a marked improvement of hepatic function occurred, together with regeneration of hepatic parenchyma, as observed by repeated punch biopsies of the liver. Of the eight surviving cases, ascites completely disappeared in seven, and the eighth was sent, greatly improved, to a charity institution for further therapy. Two of the seven patients in whom the ascites had disappeared died later of bleeding from esophageal varices, while a third who continued to have slight jaundice went elsewhere for further therapy. The remaining four cases, which have been followed for from one and one-half to four years, are known to be alive and well

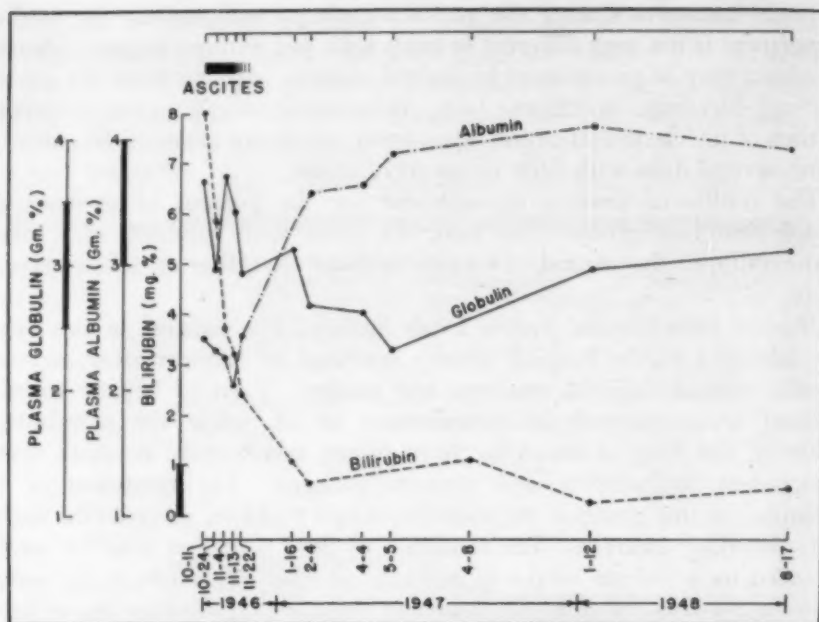


FIG. 11. Rapid disappearance of edema, ascites and jaundice, with parallel recovery of hepatic function.

without any tendency to relapse at the present time. Two of these illustrative cases follow:

CASE REPORTS

Case 1 (figure 11). A 48 year old white female bartender stated that she had consumed one-pint of liquor daily for seven years preceding admission. In January, 1945, she developed mild jaundice and pain in the right upper abdominal quadrant, and a cholecystectomy was done at another institution. The jaundice slowly disappeared. In January, 1946, the abdomen enlarged rather abruptly, the urine was dark, and the stools light-colored. She was hospitalized elsewhere for four weeks. Repeated paracenteses were done at intervals of eight days to five weeks. The patient had no appetite; she vomited frequently and lost approximately 40 pounds in weight. A mild jaundice developed at this time and increased progressively. She was first seen by us in October, 1946. The physical examination disclosed an emaciated, jaundiced patient with pitting edema of the extremities and marked ascites. The liver and spleen were not palpable. The blood counts were normal. The Wassermann and Kahn reactions were negative. The liver tests disclosed marked impairment of hepatic function. The direct reacting bilirubin was 5.8 and the total bilirubin was 8 mg. per cent; total protein 6.17 gm. per cent, albumin 2.53, and globulin 3.64; the total cholesterol 130, and the cholesterol esters 60 mg. per cent; the prothrombin time 53 per cent of normal, the alkaline phosphatase 6.3 units, cephalin-cholesterol flocculation 4 plus, thymol turbidity above 15 units, urinary urobilinogen 28 mg. per 24 hours, the fecal urobilinogen 190 mg. per 24 hours; and hippuric acid elimination 0.1 gm. The patient was given 3,000 c.c. of 5 per cent dextrose in distilled water daily and, on two occasions, 1,500 c.c. of saline. The daily output of

urine varied from 200 to 400 c.c. By paracentesis, 2,500 c.c. of ascitic fluid were removed.

On October 18 she became disoriented and two days later lapsed into a coma which persisted for four days. Plasma (500 c.c.) and dextrose in distilled water (1,500 c.c.) were administered intravenously daily. Mercupurin did not produce any diuretic effect. Improvement was noted on October 25. The coma disappeared, the appetite returned, and the patient was soon able to take 2,000 calories with 90 gm. of proteins and 300 gm. of carbohydrates daily. This diet was supplemented with 6 gm. of choline chloride daily. The jaundice gradually disappeared. The ascites was still present at the time of discharge from the hospital on November 23, 1946. Therapy subsequently consisted of a 3,500 calorie diet with 150 gm. of protein, 400

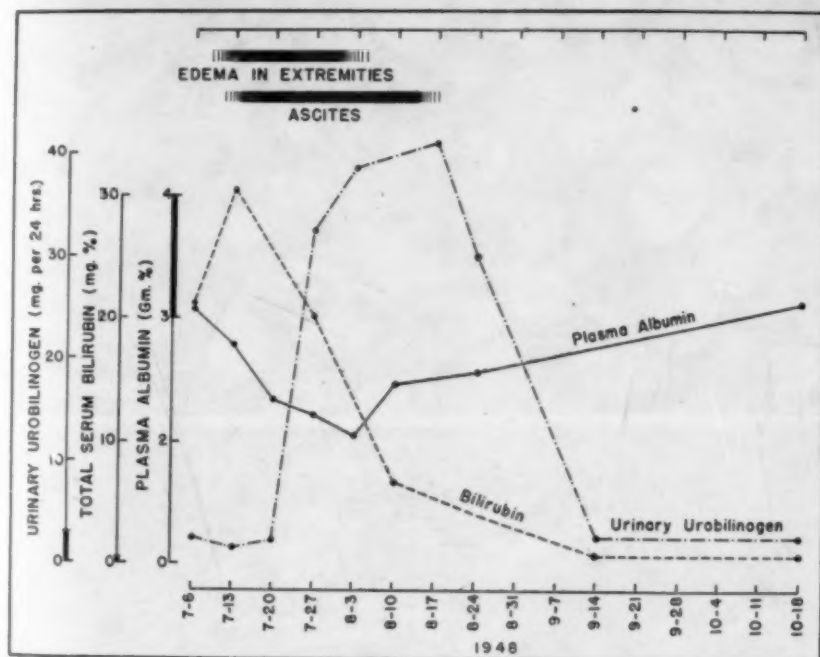


FIG. 12. Dramatic disappearance of edema, ascites and jaundice, with marked and sustained recovery of parenchymal function.

gm. of carbohydrate, 133 gm. of fat, and 6 gm. of choline chloride. She received an injection of mercupurin twice a week, then once a week until the ascites disappeared.

The patient has been seen repeatedly in the outpatient clinic during the last three and one-half years. The liver tests have become normal except for the continued moderate retention of bromsulfalein (25 to 35 per cent). She has been entirely free of symptoms from December, 1946, to the present time, April, 1950. She has become obese, with an increase of nearly 70 pounds in weight.

Case 2 (figures 12 and 13). A 46 year old white male schoolteacher had been an alcoholic for many years. He was first seen in the Neurology Clinic in 1944 because of a marked tremor of the hands and tongue and mental confusion following acute alcoholic intoxication. These symptoms disappeared after several days.

Hospitalization was necessitated on July 16, 1946, by delirium after intoxication, and again in December, 1946, because of paraldehyde intoxication. In the following months he was re-admitted frequently because of acute alcoholic episodes; on one occasion he had a convulsive state. In June, 1948, he became fatigued, lost his appetite, and was unable to continue his work.

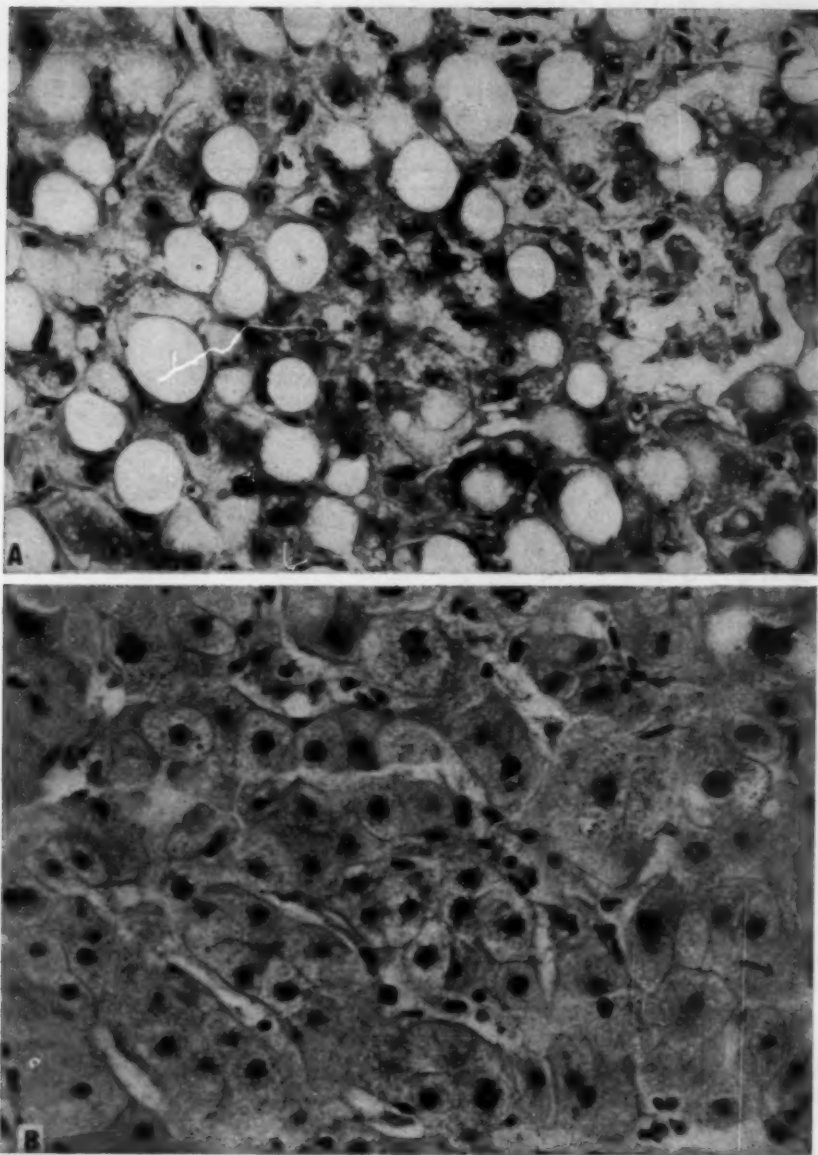


FIG. 13. Photomicrographs of punch liver biopsies during severe parenchymal failure (a) and, 82 days later, after clinical recovery (b).

He was re-admitted to the hospital on July 3, 1948, after having vomited nearly 300 c.c. of bloody gastric contents. He was unconscious for a short time and his blood pressure had dropped to 104 mm. Hg systolic and 74 mm. diastolic. He was deeply icteric; there were marked tremors of the hands and tongue. The liver was palpated four centimeters below the costal margin in the right midclavicular line, the spleen could not be felt, and there was no ascites or edema of the extremities. The erythrocyte count was 3.0 million per cu. mm., the hemoglobin was 11.5 gm. per cent. The feces were strongly positive for occult blood. The non-protein nitrogen was 28 mg. per cent; renal function as measured by the urea clearance test was normal. The urine contained bile. The liver tests indicated marked impairment of hepatic function; the direct reacting bilirubin was 15.5 and the total bilirubin 22 mg. per cent; total cholesterol was 140 and cholesterol esters 40 mg. per cent; total proteins 6.24 gm., albumin 3.16, and globulin 3.08; prothrombin time 66 per cent, alkaline phosphatase 9.5 units, cephalin-cholesterol flocculation 3 plus, and thymol turbidity 12.5 units; no urinary or fecal urobilinogen was present; hippuric acid elimination was 0.4 gm.

The patient was given 3,000 c.c. of 5 per cent dextrose, 500 c.c. of whole blood, and a diet of 350 gm. of carbohydrate, 100 gm. of protein, the remaining calories being made up by fat, and 6 gm. of choline chloride daily. In the following days he remained severely ill and ate only about one-third of his diet. The jaundice increased and the stools continued to be positive for occult blood.

Edema of the extremities appeared, followed by ascites; the jaundice increased, and the stools continued to be clay-colored. The appetite was very poor, but there was a progressive gain in weight due to increased edema and ascites. Five thousand c.c. of deeply yellow ascitic fluid were removed by paracentesis. The intake of sodium was limited to 300 mg. daily. In the following days his condition remained extremely serious but the weight decreased, and soon he improved. His appetite was better and the stools became normal in color. Edema and ascites had disappeared by the day of discharge, August 16, 1948. A slight jaundice was still present. No diuretics were used, although the patient was advised to continue a low-salt diet, which included 150 gm. of protein and 300 to 400 gm. of carbohydrate daily. In August, 1948, he returned to work and has been working full time since then. The jaundice has disappeared.

Several needle biopsies of the liver disclosed progressive disappearance of the parenchymal degeneration and the fatty infiltration previously present (figure 13). The fibrosis, however, remained unaltered. Liver tests disclosed a marked improvement of parenchymal function, values returning to the normal range, with the exception of bromsulfalein retention, which remained abnormal. A severe mental depression and anxiety that apparently were the cause for his taking alcohol disappeared entirely when he changed jobs. To the best of our knowledge, he has done without alcohol from the day he left the hospital to date, December, 1949. He has also been symptom-free since then.

In this group of cases the immediate poor prognosis depends on the failure of the liver parenchyma itself; ascites is a complicating factor which can be controlled. The prognosis of the cases that survived this severe episode of "hepatitis" depended on numerous factors, e.g., the capacity of the patient to follow adequate medical management permitting liver regeneration and improvement of nutrition, and the complications of the disease, the most important of which is massive bleeding from rupture of esophageal varices.

Protein Depletion without Symptoms of Liver Failure or Jaundice: No jaundice or manifestations of hepatic failure were found in this group. The tests of hepatic function, in general, did not consistently show marked impairment; in a few it was only minimal. Morphologic studies of the liver tissue obtained by punch liver biopsy failed to disclose severe degenerative or necrotic changes of the parenchyma.

From the point of view of nutrition, in cases with marked emaciation several months were necessary to improve nutrition, replete tissue proteins, and produce an elevation of the plasma proteins, together with disappearance of ascites and edema. It was extremely interesting that the elevation of plasma proteins occurred after several months of medical management, following improvement of nutrition. In the past, attempts to raise plasma proteins in patients submitted to repeated paracenteses usually were carried out for insufficient periods of time. The results were necessarily discouraging.

With an adequate oral caloric and protein intake, the need for protein infusion is doubtful, especially if such infusions carry salt in the form of plasma or protein hydrolysate. Salt-poor human albumin infusions may, however, considerably shorten the period of hospitalization.

In this group of 14 cases, ascites disappeared in 10. Of the remaining four, one died from esophageal bleeding soon after treatment was begun; another became psychotic and had to be transferred to another institution; a third, unable to follow the diet, continued to have ascites, and later died elsewhere; the fourth underwent an omentopexy and died five days later with liver failure, jaundice and oliguria. Of the 10 patients in whom ascites disappeared, three subsequently died of massive bleeding from esophageal varices without recurrence of edema or ascites; one was free of symptoms, edema and ascites for four months and then developed abdominal pain and fluid in the abdomen and died. At autopsy, this patient was found to have a diffuse subacute peritonitis of unknown cause. A fifth patient had two recurrences of bleeding from ruptured esophageal varices but no recurrence of edema or ascites; we are no longer in touch with her. The remaining five cases are known to be alive and without recurrence of ascites after six months to five years.

It appears that the main problem in the medical management of this group of cases is improvement of nutrition sufficient to bring about spontaneous increase of plasma albumin and disappearance of edema and ascites. Patients who discontinued alcohol and who maintained an adequate nutrition showed no tendency to relapse. The prognosis of the ascites was encouraging, but the ultimate prognosis of the disease itself hinged to a great degree on the complications, the most frequent cause of death being bleeding from esophageal varices.

DISCUSSION

The rôle of nutrition and proteins in the pathogenesis of portal cirrhosis is further emphasized in the present study. Post and Patek⁵ related ascites to a deficit in plasma albumin, with consequent decrease of the colloid osmotic pressure of the blood. In the present study, in the untreated cases with and without ascites, overlapping values of total plasma proteins and plasma globulin were found, but striking differences were seen in the plasma albumin which largely determines the colloid osmotic pressure of the blood. This is in agreement with previous observations.^{5, 9, 29} Indeed, the mean value of total proteins in cases of cirrhosis without ascites was slightly higher than that in normal controls in this series, due to elevation of the globulin fraction (table 1). Similar observations have been made by Bjorneboe⁸ in virus hepatitis. Marked hypoproteinemia and edema have been described in prolonged inanition.^{52, 53, 54, 55, 56} Weech et al.⁵⁷ demonstrated retention of fluid in the body paralleling the lowering of plasma albumin. "Critical levels" for edema and ascites varied experimentally in dogs with malnutrition and after plasmapheresis,^{57, 58, 59} in nephritis,^{60, 61} and in cases of portal cirrhosis.^{5, 29} The evaluation of the concentration of plasma proteins is very hazardous unless account is taken of the shift of the body fluids. "Critical levels" of plasma albumin or colloid osmotic pressure of plasma are in themselves too simple an explanation for the very complex mechanism involved in the formation of edema and ascitic fluid. That the lowering of the colloid osmotic pressure of plasma is not solely responsible for the retention of fluid is demonstrated in the present study following salt-poor human albumin infusions to patients maintained with a sodium intake of 2,400 mg. daily. The administration of such protein alone did not significantly change the tendency to retention of fluid when excretion of sodium in the urine was inadequate. The immediate effects of parenteral protein infusions in cases with poor elimination of salt depended on the daily sodium intake. In recent years it has been demonstrated that patients with ascites have a marked impairment in the excretion of sodium. This lack of elimination of sodium was not found in our experience¹² in portal cirrhosis without edema and ascites, nor in those who had recovered from edema and ascites. Ralli et al.⁶ also have demonstrated that the urine of patients with ascites possesses a marked antidiuretic effect when injected into hydrated rats. They found, again, that there is little or no increase of an antidiuretic substance over the normal in the urine of patients with portal cirrhosis without ascites. Normal urine has only a slight antidiuretic activity. The rôle of the kidney tubules in the retention of salt and water is extremely important, and no adequate explanation has been given to date. The present observations seem to indicate that it is imperative to replete proteins and to improve nutrition in cases with edema and ascites while maintaining a strict control of the fluid balance by restricting sodium intake.

By these means, paracentesis may be avoided. It seems that the reduction of albumin in the blood, except for acute cases, occurs only when the protein stores are depleted.

In a previous study it was demonstrated that the symptoms of parenchymal liver failure and the measurable impairment of hepatic function did not correlate with the degree of fibrosis of the liver.⁶² This study does not support the theory that ascites is brought about by the progressive mechanical obstruction produced by liver fibrosis leading to "portal hypertension," portal stasis, and formation of ascitic fluid. According to the latter view, relief of the obstruction of the portal vein by establishing collateral anastomosis through portal shunts is indicated. The result of this type of surgery has been previously covered.^{63, 64} Volwiler, Grindlay and Bollman⁶⁵ have demonstrated that portal vein hypertension is not an essential factor to the formation of ascites in the dog. Furthermore, it appears that shunts, or Eck's fistulae, are procedures that lead to hypoproteinemia and impairment of the regeneration of liver parenchyma. It would seem that, if increased tension of the portal circulation were the primary factor, all patients with portal cirrhosis would develop ascites. The absence of this correlation would suggest, therefore, that increase of tension in the portal vein may play an adjuvant rôle in localizing the accumulation of fluid in the abdominal cavity but is not the primary cause of its formation. The present data, together with the fact that ascites and peripheral edema most frequently occur simultaneously, indicate that the accumulation of fluid is related primarily to systemic causes. Cases in which ascites has disappeared entirely following medical management do not substantiate the concept that the ascites was due to fibrosis of the liver as the latter persists unchanged.

The present study indicates that disappearance of ascitic fluid can be achieved by medical management. For patients with severe liver failure, ascites and jaundice, the treatment of the liver failure itself is the main problem, the ascites being of secondary importance and readily controlled. Death occurs in these cases from failure of the liver parenchyma. Recovery is accompanied by regeneration of liver parenchyma, improvement of hepatic function, rise of plasma albumin, and subsequent disappearance of edema and ascites. The improvement of nutrition appears to be the most important problem in cases without jaundice or parenchymal failure, and can be brought about by months of diligent medical care. The ultimate prognosis of portal cirrhosis with ascites is similar to portal cirrhosis without ascites. It rests mainly on adequate nutrition of the patient and on the complications of the disease, the most important being bleeding from varicose veins of the esophagus.

CONCLUSIONS

1. The medical management of patients with or without ascites is similar except for sodium restriction in patients with ascites.

2. Fluid retention can be controlled by restricting the intake of sodium.
3. Dietary management with a high protein, high carbohydrate and high caloric intake, plus additional choline chloride, tends to improve nutrition and hepatic parenchymal regeneration, to bring about sustained rise in plasma albumin, and thus to eliminate edema and ascites. This effect is obtained after continuous treatment for several months.
4. Plasma albumin values apparently can be restored only after repletion of tissue protein.
5. Repeated paracenteses should be avoided, since they result in a marked loss of protein.
6. No tendency to recurrence of ascites is seen in uncomplicated cases maintained on an adequate nutrition.
7. The immediate prognosis of jaundiced patients with ascites depends on the severity of the parenchymal failure.
8. The ultimate prognosis of patients who have recovered from edema and ascites remains guarded, and is determined to a great extent by the incidence of complications, the most frequent of which is bleeding from varicose veins of the esophagus.

BIBLIOGRAPHY

1. Govaerts, P.: Osmotic pressure of serum proteins, *Compt. rend. Soc. de biol.* **90**: 969, 1924.
2. Govaerts, P.: Influence of protein-globulin ratio on osmotic pressure of serum proteins, *Compt. rend. Soc. de biol.* **93**: 441, 1925.
3. von Farcas, G.: Über die Wirkung des Albumin-Globulien-Quotienten auf den osmotischen Druck des Serums, *Ztschr. f. d. ges. exper. Med.* **50**: 410, 1926.
4. Peters, J. P., and Eisenman, A. J.: The serum proteins in diseases not affecting primarily the cardiovascular system or kidneys, *Am. J. M. Sc.* **186**: 808, 1933.
5. Post, J., and Patek, A. J.: Serum proteins in cirrhosis of the liver. I. Relation to prognosis and to formation of ascites, *Arch. Int. Med.* **69**: 67, 1942.
6. Ralli, E. P., Robson, J. S., Clarke, D., and Hoagland, C. L.: Factors influencing ascites in patients with cirrhosis of the liver, *J. Clin. Investigation* **24**: 316, 1945.
7. Wies, C. H., and Peters, J. P.: Osmotic pressure of proteins in whole serum, *J. Clin. Investigation* **16**: 93, 1937.
8. Bjorneboe, M., Bran, C., and Roaschov, F.: Colloid osmotic pressure in chronic hepatitis: role in pathogenesis of ascites, *Nord. med.* **35**: 1465, 1947.
9. Butt, H., Snell, A. M., and Keys, A.: Plasma proteins in hepatic disease: a study of the colloid osmotic pressure of blood serum and of ascitic fluid in various diseases of the liver, *Arch. Int. Med.* **63**: 143, 1939.
10. Layne, J. A., and Schemm, F. R.: The use of a high fluid intake and a low sodium acid-ash diet in the management of portal cirrhosis with ascites, *Gastroenterology* **9**: 705, 1947.
11. (a) Farnsworth, E. B.: Electrolyte partition in patients with edema of various origins, *Am. J. Med.* **4**: 338, 1948; (b) Farnsworth et al., *J. Lab. and Clin. Med.* **33**: 1545, 1948; (c) Farnsworth et al., *J. Lab. and Clin. Med.* **33**: 1534, 1948.
12. Ricketts, W. E., Eichelberger, L., and Kirsner, J. B.: Unpublished data.
13. Ricketts, W. E., Kirsner, J. B., and Palmer, W. L.: The diagnostic value of liver biopsy,

- tests of hepatic function and electrophoretic fractionation of sera in asymptomatic portal cirrhosis, *J. Lab. and Clin. Med.* **35**: 403, 1950.
14. Ricketts, W. E., Kirsner, J. B., and Palmer, W. L.: Clinical observations on hepatic failure in portal cirrhosis, *Gastroenterology* **15**: 245 (1950).
 15. Ricketts, W. E., Kirsner, J. B., Palmer, W. L., and Kippen, D. D.: Tests of hepatic function in portal cirrhosis, *Gastroenterology* **15**: 40 (1950).
 16. Campbell, W. R., and Hanna, M. I.: Sulphites as protein precipitants, *J. Biol. Chem.* **119**: 9, 1937.
 17. Schade, H., and Clausen, F.: Die onkotische Druck des Blut Plasmas und die Entstehung der renalbedingten Oedeme, *Ztschr. f. klin. Med.* **100**: 363, 1924.
 18. Gilbert, A., and Chiray, M.: Diminution des substances albumineuses du serum sanguin chez les cirrhotiques ascitiques, *Compt. rend. Soc. de biol.* **63**: 497, 1907.
 19. Grenet, H.: Diminution des albumines du serum sanguin chez les hepaticques, *Compt. rend. Soc. de biol.* **63**: 552, 1907.
 20. Filinski, W.: L'augmentation du taux de la globuline dans le serum du sang comme resultat de l'insuffisance hepaticque, *Presse med.* **30**: 236, 1922.
 21. Atchley, D. W., Loeb, R. F., and Benedict, E. M.: Physical and chemical studies of human serum blood; study of miscellaneous disease conditions, *Arch. Int. Med.* **31**: 616, 1923.
 22. Abrami, P., and Wallick, R.: Modifications du serum sanguin du foie avec ascites: In version du rapport serines-globulines, *Compt. rend. Soc. de biol.* **101**: 291, 1929.
 23. Salvensen, H. A.: Variations of plasma proteins in non-renal conditions, *Acta med. Scandinav.* **72**: 113, 1929.
 24. Hand, H. M.: Concentration of serum proteins in different types of edema; illustrative cases, *Arch. Int. Med.* **54**: 215, 1934.
 25. Meyers, W. K., and Keefer, C. S.: Relation of plasma proteins to ascites and edema of cirrhosis of the liver, *Arch. Int. Med.* **55**: 349, 1935.
 26. Tumen, H., and Bockus, H. L.: Clinical significance of serum proteins in hepatic diseases as compared with other liver function tests, *Am. J. M. Sc.* **193**: 788, 1937.
 27. Foley, E. F., Keeton, A. W., Kendrick, A. B., and Darling, D.: Alterations of serum proteins as index of hepatic failure, *Arch. Int. Med.* **60**: 64, 1937.
 28. Kendall, F. E.: Studies on serum protein. I. Identification of a single serum globulin by immunological means; distribution of the sera of normal individuals and patients with cirrhosis of the liver and with chronic glomerulonephritis, *J. Clin. Investigation* **16**: 921, 1937.
 29. Dauphinee, J. A., and Campbell, W. R.: Serum proteins in hepatic disease, *M. Clin. North America* **32**: 236, 1930.
 30. Wiener, H. J., and Wiener, R. E.: Plasma proteins, *Arch. Int. Med.* **46**: 236, 1930.
 31. Rimmerman, A. B., Schwartz, S. O., Popper, H., and Steigman, F.: Dietary factors in the treatment of dietary cirrhosis with jaundice, *Am. J. Digest. Dis.* **11**: 401, 1944.
 32. Gutman, A. B.: The plasma proteins in disease, *Advances in Protein Chemistry* **4**: 221, 1948.
 33. Luetscher, J. A., Jr.: Electrophoretic analysis of the proteins of plasma and serous effusions, *J. Clin. Investigation* **19**: 313, 1940.
 34. Gray, S. J., and Barron, E. S. C.: The electrophoretic analysis of the serum proteins in diseases of the liver, *J. Clin. Investigation* **22**: 191, 1943.
 35. Ricketts, W. E., Sterling, K., Kirsner, J. B., and Palmer, W. L.: Electrophoretic studies of the serum proteins in portal cirrhosis, *Gastroenterology* **13**: 205, 1940.
 36. Sterling, K., Ricketts, W. E., Kirsner, J. B., and Palmer, W. L.: The serum proteins in portal cirrhosis under medical management. Electrophoretic studies, *J. Clin. Investigation* **28**: 1236, 1949.
 37. Hoagland, C. L., and Dietrick, J. E.: Conference on therapy; the modern treatment of cirrhosis of the liver and hepatic insufficiency, *New York State J. Med.* **43**: 1041, 1943.

38. Goldschmidt, S., Vars, H. M., and Randin, I. S.: The influence of foodstuffs upon the susceptibility of the liver to injury by chloroform and the probable mechanism of their action, *J. Clin. Investigation* 18: 277, 1939.
39. Miller, L. L., Ross, J. F., and Whipple, G. H.: Methionine and cystine, specific protein factors preventing chloroform liver injury in protein-depleted dogs, *Am. J. M. Sc.* 200: 739, 1940.
40. McHenry, G. W., and Patterson, Jean M.: Hypotrophic factors, *Physiol. Rev.* 24: 128-167, 1944.
41. Hoagland, C. L.: The therapy of liver diseases, *Bull. New York Acad. Med.* 21: 537, 1945.
42. Patek, A., Jr., and Post, J.: Treatment of cirrhosis of the liver by a nutritious diet and supplement rich in vitamin B complex, *J. Clin. Investigation* 20: 481, 1941.
43. Kunkel, H. G., Labby, D. H., Ahrens, E. H., Jr., Shank, R. E., and Hoagland, C. L.: Use of concentrated human serum albumin in treatment of cirrhosis of the liver, *J. Clin. Investigation* 27: 305, 1948.
44. Thorn, G. W., Armstrong, S. H., Jr., and Davenport, V. D.: Chemical, clinical, and immunological studies on products of human plasma fractionation; use of salt poor concentrated human serum albumin solution in the treatment of hepatic cirrhosis, *J. Clin. Investigation* 25: 304, 1946.
45. Kunkel, H. G.: Treatment of cirrhosis with concentrated human albumin solution. Conference on liver injury sponsored by the Josiah Macy, Jr. Foundation, Tr. Fifth Meet. Sept. 26-27, 1946.
46. Mankin, H., and Lowell, A.: Osmotic factors influencing formation of ascites in patients with cirrhosis of the liver, *J. Clin. Investigation* 27: 145, 1948.
47. Patek, A. J., Jr., Mankin, H., Colcher, H., Lowell, A., and Earle, D. P., Jr.: Effects of intravenous injection of concentrated human serum albumin upon blood plasma, ascites and renal functions in three patients with cirrhosis of the liver, *J. Clin. Investigation* 27: 135, 1948.
48. Armstrong, S. H., Jr.: Mechanisms of action of serum albumin therapy in internal medicine, *Am. J. Med.* 4: 390, 1948.
49. Faloona, W. W., Eckhardt, R. D., Murphy, T. L., Cooper, A. M., and Davidson, C. S.: An evaluation of human serum albumin in the treatment of cirrhosis of the liver, *J. Clin. Investigation* 28: 583, 1949.
50. Patek, A. J., Post, J., Tatnoff, O. D., Mankin, H. H., and Hillman, R. W.: Dietary treatment of cirrhosis of the liver, *J. A. M. A.* 138: 543, 1948.
51. Rowntree, L. G., Chapman, H. B., and Snell, A. B.: Cirrhosis of the liver, *Post-Grad. M. A. North America Assemb. Interstate* 6: 560, 1930.
52. Lusk, G.: Physiological effect of undernutrition, *Physiol. Rev.* 1: 523, 1921.
53. Kohman, E. A.: Experimental production of edema related to plasma deficiency, *Am. J. Physiol.* 51: 378, 1920.
54. Bruckman, F. S., D'Esopo, L. M., and Peters, J. P.: Malnutrition and the serum proteins, *J. Clin. Investigation* 8: 577, 1929-30.
55. Frisch, R. A., Mendel, J. B., and Peters, J. P.: Production of edema and serum deficiency in white rats by low protein diets, *J. Biol. Chem.* 84: 167, 1929.
56. Youmans, J. B., Bell, A., Dunley, D., and Frank, H.: Endemic nutritional edema. I. Clinical findings and dietary studies, *Arch. Int. Med.* 50: 843, 1932; II. Serum proteins and nitrogen balance, *Arch. Int. Med.* 51: 45, 1933.
57. Weech, A. A., Snelling, C. E., and Goettsch, E.: Relation between plasma protein content, plasma specific gravity and edema in dogs maintained on protein inadequate diet and in dogs rendered edematous by plasmapheresis, *J. Clin. Investigation* 12: 193, 1933.
58. Darrow, D. G., Hooper, E. B., and Cary, M. C.: Plasmapheresis edema. Relation of reduction of serum proteins to edema and pathological anatomy accompanying plasmapheresis, *J. Clin. Investigation* 11: 683, 1932.

59. Lepore, M. J.: Experimental edema produced by plasma protein depletion, *Arch. Int. Med.* **50**: 488, 1932.
60. Leiter, L.: Experimental nephritic edema, *Arch. Int. Med.* **48**: 1, 1931.
61. Moore, N. S., and van Slyke, D. D.: Relation between plasma specific gravity, plasma protein content and edema in nephritis, *J. Clin. Investigation* **8**: 337, 1930.
62. Ricketts, W. E., Lushbaugh, C. C., Kirsner, J. B., and Palmer, W. L.: Pathological observations on portal cirrhosis, *Gastroenterology* **14**: 491 (1950).
63. Henrickson, E. C.: Cirrhosis of the liver with special reference to surgical aspects, *Arch. Surg.* **32**: 413, 1936.
64. Blakemore, A. H.: Portocaval anastomosis for the relief of portal hypertension, *Gastroenterology*, **11**: 488, 1948.
65. Volwiler, W., Grindlay, J. H., and Bollman, J. H.: The relation of portal vein pressure to the formation of ascites—an experimental study, *Gastroenterology* **14**: 40, 1950.

THE EFFECT OF SOME STEROIDS (TESTOSTERONE PROPIONATE, DESOXYCORTICOSTERONE ACETATE AND ASCORBIC ACID, AND 21-ACETOXY Δ -5-PREGNENOLONE, ARTISONE ACETATE, WYETH) IN RHEUMATOID ARTHRITIS *

By H. M. MARGOLIS, M.D., F.A.C.P., and PAUL S. CAPLAN, M.D.,
Pittsburgh, Pennsylvania

THE striking observations reported by Hench, Kendall, Slocumb and Polley¹ of the beneficial effect of daily administration of 17-hydroxy-11-dehydrocorticosterone (compound E, cortisone), and of pituitary adrenocorticotrophic hormone (ACTH) in rheumatoid arthritis, have presented the brightest hope for alleviation of the manifestations of this serious disease. However, lack of sufficient knowledge of the long-range metabolic effects of these potent hormones and their present unavailability for general therapeutic use have stimulated an avid search for some related steroid which may duplicate or approach the effectiveness of the agents employed by Hench.

Testosterone propionate is a steroid chemically related to cortisone. In large doses it has been shown to produce amelioration of symptoms and to induce temporary objective improvement in some patients with metastases of bone from breast carcinoma.² These favorable effects of testosterone propionate, particularly the analgesia and the positive nitrogen balance it promotes, suggested that androgens might exert similar systemic benefit in patients with rheumatoid arthritis.

Other observers³ have written of striking therapeutic benefit from the use of desoxycorticosterone acetate; and our interest was later directed to 21-acetoxy Δ -5-pregnenolone (Artisone acetate, Wyeth) as a possible therapeutic tool in rheumatoid arthritis.

This report deals with the results of clinical and laboratory observations in a group of patients with rheumatoid arthritis who were treated with large doses of testosterone propionate, another group treated with desoxycorticosterone acetate and ascorbic acid, and a smaller group treated with 21-acetoxy Δ -5-pregnenolone (Artisone acetate, Wyeth).

In view of the interest of the practicing physician in the therapeutic pos-

* Received for publication June 17, 1950.

From the Departments of Medicine, School of Medicine, University of Pittsburgh, St. Margaret Memorial and Montefiore Hospitals, and the John C. Oliver Memorial Research Foundation of St. Margaret Memorial Hospital.

Aided by a grant from the Western Pennsylvania Chapter of the Arthritis and Rheumatism Foundation and the John C. Oliver Memorial Research Foundation of St. Margaret Memorial Hospital.

sibilities of these compounds and the clear-cut results we have observed, we felt a report of our findings was justified.

TESTOSTERONE PROPIONATE

Since our study was begun, Ishmael et al.⁴ have reported on the use of testosterone propionate combined with estradiol benzoate and pregnenolone in the treatment of 90 patients with rheumatoid arthritis, as well as in six patients with shoulder-hand syndrome, four patients with "chronic" tophaceous gouty arthritis, and two patients with rheumatic fever. The course of the disease, they reported, was favorably altered in 81 of the 90 patients with rheumatoid arthritis, and in each of the patients with the other syndromes. The response to testosterone propionate was prompt, and apparently the androgen was the most effective of the steroids.

Clinical Material. We have investigated the effects of large doses of testosterone propionate * in 31 patients with rheumatoid arthritis. Twenty-five of the 31 patients were females. All patients presented the typical clinical picture of generalized rheumatoid arthritis of varying degrees of activity. With the exception of two patients in whom the disease had existed for one month and six months, respectively, the disease had been present for from one year to as long as 27 years. Every patient presented the usual systemic symptoms of weakness, fatigue, weight loss and anorexia, and complained of varying degrees of pain in many joints. Swelling or thickening of the periarticular structures was noted in more than one joint in every patient. With the exception of two patients, the sedimentation rate in each case was markedly accelerated, and in 15 patients there was a hypochromic anemia. Nearly every patient in this series had been under our own direct medical observation for long periods of time. They had previously received treatment either in the hospital or in the out-patient department, but either had not responded favorably or were in a state of relapse. The course of the disease in each case was sufficiently well known so that the effect of testosterone propionate alone could be accurately evaluated.

Dosage of Testosterone Propionate. Testosterone propionate was administered continuously for periods of from two to 10 weeks, in doses varying from .050 gm. every other day to .300 gm. daily for a total cumulative dose of from .600 gm. to 7.500 gm. The dose of testosterone propionate was established empirically. If no benefit was noted with a dose of .050 gm. every other day, the dose was increased to .100 gm., .200 gm., and in two cases to .300 gm. daily. The individual dosage in most cases was as large as, or larger than, that recommended for metastatic carcinoma of the breast.

* We are indebted to Dr. Cornelius H. Sullivan, of Ciba Pharmaceutical Products, for supplies of testosterone propionate (Perandren), and to Dr. Kenneth W. Thompson, of Organon, Inc., for the supplies of testosterone propionate (Neo-hombreol) used in these studies.

Results. The influence of testosterone propionate was gauged by (1) systemic improvement, which included improved sense of well being, lessening of fatigue and weakness, and improvement in appetite, (2) subsidence of pain, (3) lessening of joint swelling, (4) improvement in the sedimentation rate, and (5) improvement in the red blood cell count and hemoglobin concentration.

In 11 of the 31 cases there was marked systemic improvement; in eight, the systemic improvement was classified as only fair; in 12, no systemic benefit was noted. Systemic improvement, when it occurred, was unquestionable and consisted of alleviation of fatigue and weakness, improvement in appetite and in the feeling of well being. Marked subsidence of pain occurred in eight of the 31 patients; in eight patients, relief of pain was only fair; in 15 cases, the severity of pain was unaltered, or worse. In no case

TABLE I
Summary of Results of Treatment with Testosterone Propionate

	Degree of Improvement	Number of Patients
Systemic	Marked	11
	Fair	8
	None	12
Pain	Marked	8
	Fair	8
	None	15
Objective	Marked	0
	Fair	3
	None	28
Sed. Rate	Marked	1
	Fair	8
	None	21
RBC	Marked	0
HB	Fair	1
	None	14

was there any marked reduction in swelling of the joints, and in only three instances was there slight reduction in joint swelling. Marked improvement in the sedimentation rate was noted in only one instance; in this case there was no relief of pain and only fair systemic improvement. Of the 14 patients who had accompanying hypochromic anemia, only one showed a minor degree of improvement in the erythrocyte count and hemoglobin (tables 1 and 2).

The total dose and duration of treatment with testosterone propionate were essentially the same for those patients who showed subjective improvement and for those in whom the drug produced no beneficial effect. In the 11 cases showing marked systemic response, improvement appeared within the first few days after institution of treatment. After discontinuing testosterone propionate, systemic relapse developed within several days to one week in five patients, and after three to four weeks in two others. To date,

TABLE II
Protocol of Patients Treated with Testosterone Propionate

Patient	Sex	Duration of Arthritis, Years	Improvement					Total Dose of Testosterone, Grams	Duration of Treatment, Weeks
			Systemic	Pain	Objective	Sed. Rate	RBC-HB		
C. B.	F	3½	++	++	0	+	—	5.350	6
J. S.	M	1	++	++	0	0	0	6.600	4
J. D.	F	2½	++	++	0	+	—	1.350	9
A. M.	F	3	++	++	0	0	—	1.200	2
E. C.	F	7	++	++	+	0	0	2.600	2
S. M.	F	6	++	++	+	0	+	2.100	8
A. B.	F	½	++	++	0	+	0	2.700	3
R. P.	F	1	++	+	0	0	—	1.400	4
F. A.	F	27	++	++	+	+	—	1.150	10
F. K.	F	10	++	+	0	+	0	2.150	6
H. S.	F	4	++	0	0	0	—	2.100	2
E. T.	F	1½	+	+	0	+	—	1.650	5
H. G.	F	7	+	+	0	0	0	3.300	7
R. K.	M	7	+	+	0	0	—	7.500	5
D. M.	F	2	+	+	0	0	0	.600	1
C. S.	M	2½	+	+	0	0	—	1.500	4
M. D.	F	13	+	0	0	0	0	2.800	8
A. D.	F	7	+	0	0	0	0	7.225	8
N. C.	F	6	+	0	0	++	0	2.100	2
R. F.	M	12	0	+	0	+	—	2.000	2
C. C.	F	8	0	0	0	0	—	2.100	3
M. N.	F	1/12	0	0	0	+	0	1.500	5
K. M.	F	7	0	0	0	0	—	2.700	6
E. C.	F	4	0	0	0	—	—	4.500	3
L. W.	F	1	0	0	0	0	0	1.500	2
M. H.	F	2	0	0	0	0	0	2.100	2
C. P.	M	2½	0	0	0	0	0	.600	1
M. S.	F	3	0	0	0	0	—	.800	4
M. M.	F	10	0	0	0	0	0	1.450	5
A. B.	F	8	0	0	0	0	—	1.450	8
H. D.	M	8	0	0	0	—	—	.900	3

CODE OF REFERENCE

Clinical

0..... No improvement
+..... Fair improvement
++..... Marked improvement

Sed. Rate

0..... No change
+..... 5-10 mm. slower
++..... Over 10 mm. slower
—..... No elevation of sed. rate

RBC and HB

0..... No change
+..... 10% improvement in HB
+..... 1 million improvement in RBC
++..... Over 10% improvement in HB
+..... Over 1 million improvement in RBC
—..... No initial anemia

one patient has been observed for three months and three patients for six to seven months, with maintenance of systemic improvement. In relapse, after discontinuing testosterone propionate, pain reappeared as the first symptom. In practically every case there was some weight gain, which was lost, in most instances, after cessation of treatment.

Control Observations. Four patients who had obtained marked systemic improvement and relief of pain with testosterone propionate were given injections of sesame oil as controls. In one of these patients, whose improvement was being maintained by weekly injections of testosterone propionate, recurrence of symptoms developed within two weeks of substitution of sesame seed oil. With resumption of treatment with testosterone propionate, symptomatic remission was again induced. The second patient, whose improvement was being maintained by weekly injections of testosterone propionate, relapsed after three weeks of treatment with sesame seed oil. In the third patient, the placebo of sesame seed oil was given during the period of relapse after stopping testosterone propionate, without beneficial effect. Upon resuming testosterone propionate again, the systemic improvement and relief of pain which had accompanied the initial course of testosterone therapy could not be reproduced. The fourth patient, who developed recurrence of symptoms after discontinuing testosterone propionate, was given injections of sesame seed oil without benefit.

Side Effects of Androgen Therapy. Undesirable side effects, consisting of evidences of masculinization, menstrual disturbances, and rounding of the facies, occurred to some degree in most of the women. Several patients developed edema of the ankles. The incidence or severity of side effects was no greater in those patients receiving the larger, than in those receiving smaller, doses of testosterone propionate.

SUMMARY AND DISCUSSION

It is significant that, despite systemic improvement of either marked or fair degree in 19 and relief of pain of some degree in 16 of the 31 patients, there was little or no accompanying change in joint swelling, or improvement in the sedimentation rate or erythrocyte count and hemoglobin. The absence of objective evidence of remission in the arthritis, despite the favorable systemic metabolic effects induced by testosterone propionate in some patients, indicates that this steroid cannot be considered a specific therapeutic drug in rheumatoid arthritis. Undoubtedly, some of the systemic improvement is related to a favorable influence of the drug on metabolic processes. The loss of weight promptly following discontinuance of testosterone propionate indicates that most of the weight gained under treatment is probably the result of electrolyte and water retention, rather than actual improvement in nutrition. Thus, the influence of androgen therapy is not nearly so striking in rheumatoid arthritis as are its reported metabolic and analgesic effects in patients with metastatic carcinoma of the breast.

The control observations with injections of sesame seed oil in four patients who had reported subjective improvement under treatment with testosterone propionate, and none while they were given sesame seed oil, would suggest that the improvement noted in these cases was actually attributable to the effect of the androgen.

Our experience forces us to the conclusion that, although the administration of testosterone propionate may be of some value in a few selected cases of rheumatoid arthritis with marked systemic symptoms in whom some temporary amelioration of the subjective manifestations may be obtained, the inconstancy of this effect, the relapses that occur promptly in most instances following discontinuance of treatment, and the incidence of undesirable side effects indicate that androgen therapy has little, if any, promise in the treatment of rheumatoid arthritis.

THE EFFECT OF DESOXYCORTICOSTERONE ACETATE AND ASCORBIC ACID

A recent report by Lewin and Wassen³ of spectacular beneficial effects in rheumatoid arthritis from the combined use of desoxycorticosterone acetate in oil injected intramuscularly, followed immediately by an intravenous injection of one gram of ascorbic acid, suggested another possible approach to practical therapy. Despite the previous demonstration of Selye⁵ that desoxycorticosterone acetate was a potent factor in inducing articular disease in rats, it appeared of sufficient practical importance to observe whether the results reported by Lewin and Wassen could be confirmed.

Clinical Material. Twenty-eight patients were treated with injections of desoxycorticosterone acetate and ascorbic acid. All of these patients suffered from typical generalized active rheumatoid arthritis of three months' to 24 years' duration. They presented varying degrees of joint involvement, ranging from early periarticular swelling, without significant changes in the cartilaginous and bony structures, to advanced destructive changes in joints with deformities. In all instances there was an accompanying acceleration of the sedimentation rate and the usual systemic manifestations. Desoxycorticosterone acetate was administered intramuscularly in a dosage of .005 gm., followed immediately by 1.0 gm. of ascorbic acid, intravenously.* The patients were observed for at least one hour after each treatment. Further evaluation of the effect of the injection was based upon the descriptive statement of the patient and the findings on examination at the subsequent visit.

Clinical Results. Of the 28 patients treated, only four showed "marked" improvement, and in four others the improvement was classified as "fair."

* Dr. W. Alan Wright, of Schering Corporation, kindly supplied some of the desoxycorticosterone acetate (Cortate) and ascorbic acid. Percorten, desoxycorticosterone acetate (Ciba), was also employed interchangeably with Cortate.

TABLE III

Summary of Results of Treatment with Desoxycorticosterone Acetate with Ascorbic Acid

Subjective	Degree of Improvement		Number of Patients
	Marked	Fair	
	Marked	Fair	None
	Marked	Fair	None

TABLE IV

Protocol of Patients Treated with Desoxycorticosterone Acetate and Ascorbic Acid

Name	Sex	Duration of Arthritis: Years	Number of Injections	Frequency of Injections	Preparation	Improvement		Remarks
						Subjective	Objective	
M. M.	F	1	1		Percorten	++	+	Relief of pain and increased mobility of the knees
M. H.	F	2	6	Daily	Percorten and Cortate	++	0	Improvement appears in 2 hours and lasts 6 hours. Two injections without vitamin C equally effective and 2 injections of sesame oil nearly as effective
T. G.	F	10	3	Daily	Cortate	++		Practically complete relief of pain for several weeks after first injection. Similar relief after placebo
K. T.	F	8	9	Daily	Percorten and Cortate	++	0	Relief of pain and stiffness for 4 hours after each injection. No improvement with placebo
A. D.	M	3	4	Every 4 to 7 days	Cortate	+		Improvement for several hours to 5 days after each injection. Two injections without vitamin C equally effective
A. T.	F	10	5	Every 4 to 7 days	Cortate and Percorten	+	0	Improvement for several days after last injection
G. F.	M	7	5	Every 2 to 7 days	Percorten and Cortate	+	0	Improvement for 6 hours after each injection
M. M.	F		1	Weekly	Percorten	+	0	
M. D.	F	14	2	Weekly	Percorten	0	0	
E. S.	F	6	2	Weekly	Percorten	0	0	Worse for several days after each injection
G. M.	M	10	3	Weekly	Percorten	0	0	
R. Mc.	F	4	3	Weekly	Cortate	0	0	Progressively worse after each injection
F. T.	F	6	5	Daily	Cortate	0	0	

TABLE IV—Continued

Name	Sex	Duration of Arthritis: Years	Number of Injections	Frequency of Injections	Preparation	Improvement		Remarks
						Subjective	Objective	
H. D.	M	8	10	Daily	Cortate	0	0	Worse while receiving injections
E. C.	F	6	2	Daily	Cortate	0	0	
M. M.	F	10	1		Cortate	0	0	
E. E.	M	17	1		Cortate	0	0	
J. D.	M	1/3	2	Daily	Percorten	0	0	
R. K.	M	8	3	Daily	Cortate	0	0	
S. S.	F	2	2	Daily	Cortate	0	0	
R. A.	M	24	2	Daily	Cortate	0	0	
C. P.	M	2½	6	Twice daily	Cortate	0	0	
L. R.	F	10	3	Daily	Percorten and Cortate	0	0	
S. B.	M	9	1		Cortate	0	0	Worse while receiving injections
E. T.	F	2	6	Daily	Cortate	0	0	
I. W.	F	6½	2	Weekly	Cortate	0	0	
J. S.	M	1	1		Cortate	0	0	
A. D.	F	6½	1		Cortate	0	0	

CODE OF REFERENCE

Clinical

0..... No improvement
 +..... Fair improvement
 ++..... Marked improvement

Sed. Rate

0..... No change
 +..... 5-10 mm. slower
 ++..... Over 10 mm. slower
 -..... No elevation of sed. rate

RBC and HB

0..... No change
 +..... 10% improvement in HB
 1 million improvement in RBC
 ++..... Over 10% improvement in HB
 Over 1 million improvement in RBC
 -..... No initial anemia

In only one of the patients was there any objective improvement. One patient with generalized rheumatoid arthritis and Parkinsonism described complete relief of pain for several weeks after the first injection of desoxycorticosterone acetate and ascorbic acid. Upon recurrence of the symptoms, a subsequent injection of a placebo consisting of 1.0 c.c. of sesame seed oil intramuscularly and 5.0 c.c. of a normal saline solution intravenously was followed immediately by an identical degree of "complete relief of pain," which likewise persisted for several weeks. In a second patient who experienced marked relief of pain and stiffness, appearing two

hours after the injection and lasting for six hours, equally effective improvement was obtained by the administration of desoxycorticosterone acetate without ascorbic acid, as well as after two intramuscular injections of 1.0 c.c. of sesame oil without ascorbic acid. A third patient manifested marked subjective improvement and had persistent relief of symptoms along with increased mobility of the knees after one injection, but without any change in the synovitis. A fourth patient had relief of pain and stiffness for about four hours after each injection. This patient was given nine daily treatments; the most striking response occurred after the first three injections, with progressive decrease in the degree of improvement after each subsequent injection. In this patient the administration of a placebo was not accompanied by any improvement. In four patients a fair degree of subjective improvement developed after treatment. In each of these there was some relief of pain and stiffness for from several hours to as long as several days after each injection. There was no noticeable improvement in the systemic manifestations in any of these eight patients: no lessening of fatigue, and no improvement in appetite or in the sense of well being.

Four patients complained of increase in joint pain while receiving injections of desoxycorticosterone and ascorbic acid, and in two of these there was objective evidence of increased joint swelling (tables 3 and 4).

As a further control, seven patients with nonrheumatoid skeletal disorders were treated with desoxycorticosterone acetate and ascorbic acid. Three of the patients had osteoarthritis of the knees, one osteoarthritis of the cervical spine, and three adhesive peri-arthritis of the shoulder. The four patients with osteoarthritis and one of the patients with peri-arthritis of the shoulder reported subjective improvement for several hours after injections of desoxycorticosterone acetate and ascorbic acid.

SUMMARY AND DISCUSSION

Our observations on the effect of the combined use of desoxycorticosterone acetate and ascorbic acid do not confirm the described observations of Lewin and Wassen. The subjective improvement reported by some patients may be related to the psychogenic influence of "an injection of a hormone," for some of these patients respond equally well to the injection of desoxycorticosterone acetate alone or to the injection of a placebo of sesame seed oil. There may be justification for further exploration of the possible effect of desoxycorticosterone acetate and ascorbic acid in rheumatoid arthritis. Our observations would indicate, however, that recommendation of these drugs as a clinical therapeutic procedure in rheumatoid arthritis is unwarranted. We feel so especially in view of the recognized risk of disturbance of electrolyte and water metabolism which may follow long-continued administration of desoxycorticosterone acetate.

21-ACETOXY Δ -5-PREGNENOLONE

Clinical Material. 21-acetoxy Δ -5-pregnenolone (Artisone, Wyeth)* was administered to five patients with rheumatoid arthritis. These patients had typical active generalized rheumatoid arthritis with accompanying systemic manifestations. The sedimentation rate was accelerated in four of the five patients, and in three of them there was a hypochromic anemia. The duration of the arthritis varied from four months to 20 years. Artisone was administered intramuscularly in the following dosage: one patient received 0.3 gm. daily for 20 days; the second patient, 0.3 gm. daily for 10 days; the third patient, 0.3 gm. daily for eight days; the fourth, 0.1 gm. daily for nine days; the fifth, 0.3 gm. daily for three days.

Clinical Results. In none of the five patients studied was there any evidence of subjective or objective improvement. There was no relief of joint pain or stiffness, no lessening of joint swelling, no increased mobility of joints, and no improvement in the systemic manifestations. The sedimentation rate was unaffected, and the erythrocyte count and hemoglobin concentration showed no alteration. There was no change in the total circulating eosinophil counts.

To three of these five patients we* subsequently administered pituitary adrenocorticotrophic hormone (ACTH)† with striking benefit resulting promptly in each case: complete relief of articular pain, tenderness and stiffness, subsidence of joint swelling, increased range of mobility of joints, marked improvement in agility, and alleviation of systemic manifestations. The accelerated sedimentation rate in all of the three cases receiving ACTH returned to normal. In each instance there was a marked fall in the circulating eosinophils, indicating stimulation of the adrenal cortex.

SUMMARY AND DISCUSSION

Administration of 21-acetoxy Δ -5-pregnenolone (Artisone, Wyeth) to five patients with rheumatoid arthritis, in the cumulative dosage of 0.9 to 6.0 gm. given over periods of three to 20 days, was without significant effect on the clinical manifestations of the disease. It need hardly be emphasized that final conclusions cannot be drawn with regard to the effectiveness of this drug in rheumatoid arthritis. The group of patients is too small, the duration of treatment perhaps too brief, and the total dosage possibly inadequate. These results are presented at this time to contrast the ineffectiveness of acetoxy pregnenolone with the dramatic improvement in both subjective and objective manifestations of the rheumatoid process in the three patients subsequently treated with pituitary adrenocorticotrophic hormone (ACTH).

*Dr. G. E. Farrar, Jr., of Wyeth, Inc., kindly offered the supply of Artisone for this study.

†We are indebted to Dr. John R. Mote, of the Armour Laboratories, for the supplies of ACTH used in this study.

CONCLUSIONS

1. Study of 31 patients with rheumatoid arthritis treated with testosterone propionate indicates that this steroid has no specific beneficial effect in this disease.

2. A combination of desoxycorticosterone acetate and ascorbic acid in the treatment of 28 patients with rheumatoid arthritis was without significant benefit. The observations of Lewin and Wassen concerning the effectiveness of this form of therapy could not be confirmed.

3. 21-acetoxy Δ -5-pregnenolone given to five patients with rheumatoid arthritis was without value when compared to the striking effectiveness of pituitary adrenocorticotrophic hormone (ACTH) subsequently administered to three of these five cases.

BIBLIOGRAPHY

1. Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: A hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: compound E) and of pituitary adrenocorticotrophic hormone on rheumatoid arthritis. Preliminary report, Proc. Staff Meet., Mayo Clin. **24**: 181, 1949.
2. Adair, F. E., Mellors, R. C., Farrow, J. H., Woodard, H. Q., Escher, G. C., and Urban, J. A.: The use of estrogens and androgens in advanced mammary cancer, clinical and laboratory study of 105 female patients, J. A. M. A. **140**: 1193, 1949.
- Watson, J. R., and Fetterman, G. H.: Testosterone propionate in the treatment of advanced carcinoma of the breast, Surg., Gynec. and Obst. **88**: 702, 1949.
3. Lewin, E., and Wassen, E.: Effect of combined injections of desoxycortone acetate and ascorbic acid on rheumatoid arthritis, Lancet **2**: 993, 1949.
4. Ishmael, W. K., Hellbaum, A., Kuhn, J. F., and Duffy, M.: The effects of certain steroid compounds on various manifestations of rheumatoid arthritis. A preliminary report, J. Oklahoma M. A. **42**: 10, 1949.
5. Selye, H., Sylvester, O., Hall, C. E., and Leblond, C. P.: Hormonal production of arthritis, J. A. M. A. **124**: 201-207, 1944.
6. Unpublished data.

OBESITY IN DIABETES: A STUDY OF THERAPY WITH ANOREXIGENIC DRUGS *

By KERMIT E. OSSERMAN, M.D., and HENRY DOLGER, M.D., F.A.C.P.,
New York, N. Y.

IN the treatment of the obese diabetic, management of the obesity is secondary to insulin in the control of diabetes mellitus. Mirsky¹ considers the obese diabetic as being "decompensated" with a relative or absolute insulin insufficiency. With decreased caloric intake and consequent weight reduction, the patient may be restored to "compensation" and the insufficiency of insulin can equal the reduced metabolic demand. If the diabetic patient remains obese, not only may the control of the diabetes become more and more difficult, but reduction in weight eventually may not be effective in restoring carbohydrate tolerance.² The relative insufficiency of insulin then becomes an absolute one, and such patients require insulin.

According to Newburgh and Conn,³ Handelsman,⁴ and John,⁵ weight reduction not only decreases hyperglycemia and glycosuria but, not infrequently, may even restore normal glucose tolerance. Similar observations have been made by Fetter, Durkin and Duncan,⁶ who conclude that the majority of obese diabetic patients do not need insulin if sufficient weight reduction can be achieved.

The excellent results reported by Newburgh and Conn³ contrast with those of the average physician who obtains coöperation only in the minority of obese patients. Danowski and Winkler⁷ reported 80 per cent failure in the long-term dietary treatment of the overweight. The difficulty in controlling such patients is understandable in the light of recent extensive reports^{8,9} on the psychic factors which lead to obesity which has been described as the "physical expression of a neurosis."¹⁰ Nicholson¹¹ states that "psychotherapy and reestablishment of proper dietary habits are essential for permanent weight reduction."

There are two adjuvant therapies available to the nondiabetic obese patient: (1) psychotherapy, and (2) the use of anorexigenic drugs.¹² The latter have been considered as being contraindicated in the treatment of the obese diabetic because of their possible hyperglycemic^{13, 14} and hypertensive¹⁵ effects.

Because of the inability to maintain adequate dietary control in a large group of obese diabetic patients, and because of the limited facilities for psychotherapy and the impracticability of its widespread application, an investigation was undertaken to study the effects of the anorexigenic drugs

* Received for publication December 21, 1948.

From the Metabolism Division of The Medical Services of The Mount Sinai Hospital, New York.

Aided by a grant from the Smith, Kline and French Laboratories.

upon these individuals. In view of the alleged contraindications to the use of these compounds in diabetes mellitus, the relatively advanced age of the patients, and the high incidence of cardiovascular damage in diabetic individuals, this study was undertaken with some hesitation. It was felt that the accelerated vascular damage¹⁶ characteristic of diabetes should be an incentive towards aggressive treatment of obesity, which is an unphysiologic state.

METHODS

Fifty-five obese diabetic patients attending the Metabolism Clinic of the Out-Patient Department of The Mount Sinai Hospital were selected for investigation. Their ages ranged from 20 to 70 years; the majority were in the age group of 45 to 64 years. Thirty-one of the patients were being treated with insulin. The remaining 24 patients had not required insulin administration. Essential hypertension was present in 30 patients.

During the period of investigation, which lasted from 18 to 30 months, each patient was examined fortnightly. The weight, blood pressure and results of fractional urinalysis for sugar were noted in the records. In patients requiring insulin, fasting blood sugar levels were determined monthly, by the micro Folin-Malmros method of blood sugar analysis. During the first 18 months of investigation, patients not receiving insulin were subjected monthly to glucose tolerance tests. In all patients, routine urinalysis and electrocardiograms were repeated at intervals during the course of therapy.

Following the initial examination, a diet of 1,000 calories was prescribed. All the patients had repeatedly failed to adhere to similarly prescribed diets. Thus, after a period of several weeks, no noticeable reduction in weight or improvement in the control of the diabetes mellitus was noted. Therefore, anorexigenic drug therapy, in the form of dl-amphetamine sulfate, "benzedrine," was included in the therapeutic regime, in doses of 5 mg. before breakfast and luncheon. This soon proved to be inadequate in most instances, and the dose was increased to 30 mg. daily (10 mg. before breakfast, before luncheon, and at 4 p.m.). After three months, three of the hypertensive patients showed further elevation of blood pressure, and d-amphetamine sulfate, "dexedrine," was prescribed in the same dosage. With this change, blood pressure returned to premedication levels in these patients. Thereafter, 48 of the 55 patients were treated with d-amphetamine sulfate. It was our experience, in this study, that equivalent anorexic effects were obtained with the same dose of either isomer.

For the past year, anorexigenic drug therapy was discontinued on all but five patients. The remaining 50 patients were continued under observation on low caloric diets. Eleven of these did not return at regular intervals, and therefore were dropped from the latter part of the investigation.

RESULTS

Thirty-six of 55 patients (65 per cent) achieved a significant weight loss of 11 to 77 pounds, with restricted caloric intake aided by anorexigenic drug therapy (table 1).

TABLE I
Amount of Weight Lost by All Patients

Weight Loss in Pounds	Number of Patients	Before Investigation	
		Patients Receiving Insulin	Patients Not Receiving Insulin
Plus-0	4	3	1
1-5	3	2	1
6-10	12 19	5 10	7 9
Significant Weight Loss	11-15	7	7
	16-20	2	4
	21-25	6	3
	26-30	2	1
	31-35	2	
	36-40	1	
	75-80	1 21	15
	55	31	24

The beneficial effect of this weight loss on carbohydrate tolerance was shown most strikingly in the 31 patients receiving insulin therapy (table 2). Of this group, 84 per cent were able to discontinue or reduce the dosage of insulin. This was a most gratifying result, especially to the 15 patients who were able to dispense with insulin entirely. Eight of these had previously required up to 25 units of insulin daily, and seven individuals had used from 25 to 70 units of insulin per day. Eleven more patients had their insulin dosage reduced by 10 to 20 units daily; in three instances, the reduction was as much as 30, 40, and 50 units per day. Fairly rapid reduction of insulin dosage was often necessary to avoid hypoglycemic reactions following marked decrease in food intake. DI-amphetamine sulfate, or its

TABLE II
Effect of Weight Loss on Insulin Dosage

Weight Loss in Pounds	No. of Patients	Patients in Whom Insulin Was Discontinued	Patients in Whom Insulin Dosage Was Reduced	Patients Who Exhibited No Change
0-10	10	2	4	4
11-20	11	5	5	1
21-30	6	4	2	
31-40	3	3		
71-80	1	1		
	31	15	11	5

isomer, did not obscure the hypoglycemic symptoms, and no difficulty was encountered in differentiating them from manifestations of drug toxicity.

In the milder group of diabetics (table 3), 32 per cent had improvement of tolerance, 7 per cent revealed further impairment and the remainder had no change, as shown by monthly glucose tolerance tests. Those showing marked improvement were in the group of patients with significant weight loss.

TABLE III
Relationship of Weight Loss to Glucose Tolerance

Weight Loss (Lbs.)	No. of Patients	Glucose Tolerance Normal or Near Normal	Glucose Tolerance Improved	Glucose Tolerance with No Change	Glucose Tolerance Worse
Plus-0	2			1	1
1-10	4			4	
11-20	13	3	1	8	1
21-30	7	1	2	4	
31-40	1	1			
76-80	1	1			
	28*	6	3	17	2

* Four of these patients originally were in the group receiving insulin.

Nineteen patients (35 per cent) could not adhere faithfully to a restricted diet despite the use of 20 to 30 mg. daily of dl-amphetamine sulfate, or its isomer, and therefore failed to lose any appreciable weight. In a few instances a paradoxical increase in appetite was noted with small doses of the drug.

TABLE IV
Weight One Year After Withdrawal of Anorexigenic Drugs

Weight Change	No. of Patients	Loss of Weight Before Withdrawal of Drugs (Over 10 lbs.)	Loss of Weight Before Withdrawal of Drugs (Less than 10 lbs.)
Further Wt. Loss in Lbs.			
1-5	6	3	3
6-10	1	1	0
Weight Gain in Lbs.			
1-5	6	4	2
6-10	10	5	5
11-15	10	6	4
16-20	5	5	
26-30	1	1	
	39	25	14

One year after anorexigenic drug therapy had been withdrawn (table 4), 19 per cent exhibited further, but minor, loss of weight, and 41 per cent regained less than 10 pounds, whereas 40 per cent of the group regained appreciable weight, from 11 to 26 pounds.

Of the 31 patients who originally required insulin, 23 have been followed for the past year. This group included 14 of the 15 patients who had discontinued insulin therapy. Table 5 shows the influence of gain in weight upon this group of patients; 50 per cent resumed insulin administration.

TABLE V
Insulin Requirement One Year After Withdrawal of Anorexigenic Drugs

Weight Gain in Pounds	No. of Patients	Insulin Initiated	Insulin Reinstigated	Increased Insulin Dose	Insulin Dose Not Changed	Omission of Insulin Continued	Further Reduction of Insulin Dose
Minus 10- 1*	5*		2			1	2
1-10	14	3	2	4	1	4	
11-20	9		3	3	1	2	
21-30	1	1					
	29†	4	7	7	2	7	2

* These five patients continued to lose weight.

† Includes two patients from table 6.

Four patients who never used insulin required it after regaining weight, and three of the four weighed more at the end than at the beginning of the study.

Table 6 shows the effects of long term therapy with anorexigenic drugs. In three patients who had almost reached their ideal weight there was no further change in weight during the course of the year. The other two

TABLE VI
The Effect of Prolonged Therapy with Anorexigenic Drugs
Continued One Year After the Original Investigation

Ideal Weight	Initial Weight	Weight at End of Investigation Period	Current Weight	Initial Dose of Insulin	Dose of Insulin at End of Investigation Period	Current Dose of Insulin
141 Lbs.	245 Lbs.	223 Lbs.	216 Lbs.	50 Units	20 Units	0 Units
144	162	151	154	15	0	0
138	169	147	147	0	0	0
144	160	146	145	0	0	0
126	193	181	165	0	0	0

patients were still losing weight, but had not approached anything near their ideal weight. The beneficial effect on carbohydrate tolerance was similar to that found in the first 18 months of investigation.

DRUG REACTIONS

A few of the patients showed reactions such as nervousness, palpitation or insomnia, which are well known side effects of anorexigenic drug therapy. Generalized dermatitis occurred in two instances. An undesirable effect on blood pressure was observed in only four patients. As already noted, an existing hypertension was aggravated in three patients by dl-amphetamine

sulfate but not by d-amphetamine sulfate. In one instance, hypertension was noted following d-amphetamine therapy, but only after the administration of a large dose (70 mg. per day). With reduction to 15 mg. per day, the blood pressure returned to its former level.

No serious complications were noted; the anginal syndrome was not provoked, nor did any instance of coronary occlusion occur. In three instances, occasional premature ventricular contractions appeared during therapy, but these extrasystoles subsided spontaneously without interruption of treatment. One patient was treated despite the existence of chronic congestive failure due to arteriosclerotic and hypertensive heart disease; hyperglycemia and glycosuria decreased with weight loss, and there was no evidence of further cardiovascular degeneration. Despite the absence of serious complications in this group, the use of anorexigenic drugs should be used cautiously in patients with significant myocardial damage.

DISCUSSION

Weight reduction in obese diabetic patients has been notoriously difficult to achieve; most need some supportive treatment. For this special type of patient, anorexigenic drugs proved valuable for short term therapy. In addition, a better transference relationship between the patient and the physician was established because of the added time and attention given each individual. An almost religious discipline and zeal had to be created in each patient for successful coöperation. While drugs were being prescribed in the first 18 months of this study, they seemed to be an answer to the problem of weight reduction in the obese diabetic individual. However, when the drug was withdrawn, the majority of patients again displayed laxity in adhering to diet control. We are not unaware of the danger of addiction to the drugs, or of their diminishing effect on prolonged use in some patients, as noted in a recent study in this hospital by Adlersberg and Mayer.¹⁷

Obese diabetic patients have an added incentive towards weight reduction in the expectation that they may be able to discontinue insulin administration. This, plus a knowledge of caloric values which is better than average, and a modicum of self-discipline essential in the management of diabetes, should effect a better result in the treatment of the obese diabetic than the non-diabetic obese individual.

We agree in spirit with Gastineau and Ryneearson,¹⁸ who object to the use of drugs in weight reduction because they divert the patient's attention from the diet. Caloric restriction should remain the basis of the treatment of obesity in diabetes mellitus. Anorexigenic drugs played no direct rôle in the improvement of carbohydrate tolerance. They simply helped 65 per cent of the group to display better coöperation in dieting, and permitted them to achieve striking reductions and even cessation of insulin therapy. Once anorexigenic drug treatment was withdrawn, only one-third of the patients continued to maintain their lower levels of weight. Thirty-eight per cent

of the patients either weighed the same or more than at the beginning of the investigation. After regaining their weight, 50 per cent of those patients who had stopped insulin therapy had to reinstitute daily injections of insulin. In this study, we found no contraindications to the use of anorexigenic drugs for the selected obese individual with diabetes mellitus.

SUMMARY

1. An investigation was undertaken to study the effect of anorexigenic drugs upon obese diabetic individuals, because of inability of these patients to maintain adequate dietary control, and because of limited facilities for psychotherapy.

2. Thirty-six of 55 obese diabetic patients exhibited significant loss of weight (11 to 77 pounds) on low caloric diets aided by anorexigenic drug therapy.

3. The most successful results were obtained in the 31 patients receiving insulin before the investigation. Fifteen patients were able to discontinue insulin administration, and 11 obtained reduction in dosage after significant loss of weight.

4. Follow-up one year after withdrawal of anorexigenic drug therapy revealed that one-third of the patients did retain their loss of weight.

5. DL-amphetamine and d-amphetamine sulfate have no direct effect upon the improvement of carbohydrate tolerance, but only an indirect one, through caloric restriction leading to weight loss.

6. No immediate adverse effects due to the amphetamines were observed in the course of the diabetes mellitus.

We acknowledge with thanks the assistance of Dr. Herbert Pollack, and the technical assistance of Alice P. Maurer, A. B., Katherina Newerly, A. M., and Beatrice Ferber, A. B.

BIBLIOGRAPHY

1. Mirsky, I. A.: Consideration of the etiology of diabetes in man, *Proc. Am. Diabetes A.* 5: 117, 1945.
2. Duncan, D. G.: *Diabetes mellitus and obesity*, 1935, Lea & Febiger, Philadelphia, p. 79.
3. Newburgh, L. H., and Conn, J. W.: A new interpretation of hyperglycemia in obese middle aged persons, *J. A. M. A.* 112: 7 (Jan. 7) 1939.
4. Handelsman, M. B.: Factors influencing the return of tolerance for glucose in middle-aged obese diabetics, *Am. J. M. Sc.* 208: 15 (July) 1944.
5. John, H. J.: Some interesting and obscure problems in diagnosis and treatment of diabetes mellitus, *Ohio State M. J.* 33: 741 (July) 1937.
6. Fetter, F., Durkin, J. K., and Duncan, C. C.: Dietary versus insulin treatment of the obese diabetic patients, *Am. J. M. Sc.* 195: 781 (June) 1938.
7. Danowski, R. S., and Winkler, A. W.: Obesity as clinical problem, *Am. J. M. Sc.* 208: 622 (Nov.) 1944.
8. Freed, C. S.: Psychic factors in the development and treatment of obesity, *J. A. M. A.* 133: 369 (Feb.) 1947.
9. Bruch, H.: Psychological aspects of obesity, *Bull. New York Acad. Med.* 24: 73 (Feb.) 1948.

10. Richardson, H. B.: Amphetamine sulphate (benzedrine) in the treatment of obesity, *New York State J. Med.* **46**: 998 (May 1) 1947.
11. Nicholson, W. M.: Emotional factors in obesity, *Am. J. M. Sc.* **211**: 443 (April) 1946.
12. Williams, R. H., Daughaday, W. H., Asper, S. P., Jr., Rogers, W. F., Jr., and Towery, B. T.: Obesity and its treatment with particular reference to the use of anorexigenic compounds, *Ann. Int. Med.* **29**: 510 (Sept.) 1948.
13. Storz, H., and Kirk, R.: Über eine neue Blutdrucksteigernde Substanz, *Deutsch. med. Wchnschr.* **63**: 393 (March 5) 1937.
14. Rao, V.: Antagonismo fra insulina e simpamina sulla pressione arteriosa e sulla glicemia, *Fra Med.* **27**: 106 (Feb. 15) 1941.
15. Detrick, L. E., Milikan, R., Modern, S. F., and Thienes, C. H.: On the pharmacology of phenylisopropylamine (benzedrine), *J. Pharmacol. and Exper. Therap.* **60**: 56 (May) 1937.
16. Dolger, H.: Clinical evaluation of vascular damage in diabetes mellitus, *J. A. M. A.* **134**: 1289 (Aug. 16) 1947.
17. Adlersberg, D., and Mayer, M. E.: Results of prolonged medical treatment of obesity with diet alone, diet and thyroid preparations, and diet and amphetamine, *J. Clin. Endocrin.* **9**: 275 (March) 1949.
18. Gastineau, C. F., and Rynearson, E. H.: Obesity, *Ann. Int. Med.* **27**: 883 (Dec.) 1947.

ELECTROCARDIOGRAPHIC PATTERNS IN STOKES-ADAMS SYNDROME *

By BERNARD H. PASTOR, M.D., *Philadelphia*, and SUZANNE H. WORRILOW, M.D., *Lebanon, Pennsylvania*

THE classical concept of Stokes-Adams syndrome is that of syncope, with or without convulsions, associated with ventricular asystole, in patients with complete A-V heart block. Morgagni¹ first described the clinical picture of this syndrome in 1761. In 1827 Adams² and in 1848 Stokes³ also described the condition, and the names of these two men are associated with it in the minds of most physicians.

For many years it was generally accepted that the mechanism underlying the clinical syndrome described by these authors and responsible for the syncope was ventricular asystole. Indeed, most textbook descriptions to-day^{4,5} are based on this classical concept of the syndrome.

In 1941, Parkinson, Papp and Evan,⁶ in an excellent analysis of all the previously reported cases, emphasized that ventricular standstill was not the only disturbance responsible for the syndrome. On the basis of electrocardiographic patterns in 56 cases which had been reported prior to that time, and eight cases of their own, they felt that the term Stokes-Adams syndrome should be applied to patients with complete heart block who suffer recurrent bouts of unconsciousness due to ventricular standstill, ventricular tachycardia, ventricular fibrillation, or a combination of these mechanisms. Of the 64 cases they analyzed, 18 showed combinations of ventricular arrhythmias and ventricular standstill, 13 showed ventricular tachycardia and ventricular fibrillation without standstill, and 33 showed ventricular standstill alone. These authors also pointed out that Stokes-Adams syncope must be differentiated from cardiac syncope occurring in patients without heart block due to ventricular standstill resulting from neurogenic (vasovagal reflexes) and myocardial causes.

The nature of the cardiac mechanism between attacks is of interest. Stokes-Adams attacks, which occur in about one-third of the cases of complete heart block, are said to be more common in partial and suddenly developing block than in established complete heart block. Nevertheless, of the 31 cases cited by Parkinson and his associates in which ventricular extrasystolic rhythms were part of the mechanism underlying syncopal attacks, only four did not show complete heart block between attacks. All of the four had some degree of partial heart block. The case which is to be presented is unusual insofar as the patient did not have established heart

* Received for publication February 1, 1949.

From the Division of Cardiology of the Philadelphia General Hospital.

block, although there was undoubtedly some damage to the A-V node, as the subsequent development of heart block would seem to indicate.

Since the publication of Parkinson's paper, Parsonnet and associates⁷ have reported a case showing all of the mechanisms described by Parkinson and his co-workers,⁶ and Schnur⁸ has reported a similar case and again re-emphasized the newer concept of this syndrome.

Although Parkinson, Papp and Evan were undoubtedly the first to define clearly the relationship of ventricular extrasystolic rhythms to the syncope of the Stokes-Adams attack, many individual observers were undoubtedly aware that ventricular arrhythmias could be responsible for the syndrome. It remained only for these authors to accumulate and analyze these isolated observations, and to bring to wider clinical recognition this viewpoint.

Lewis⁹ pointed out that there is no clear evidence that the patients described by Adams and Stokes had complete A-V block, since there are other causes of a very slow heart action. He observed also that cardiac syncope could result from various ectopic ventricular rhythms, including ventricular fibrillation. However, he did not report the occurrence of these arrhythmias in patients with complete A-V block. Although Starling¹⁰ and others recorded polygraph tracings in cases of Stokes-Adams syncope, and demonstrated that there was cessation of the pulse during the attack, such tracings did not show the exact nature of the mechanism underlying this pulseless state. Not until electrocardiographic methods were applied was it possible to record graphically the underlying mechanism. In 1922 Kerr and Bender¹¹ successfully recorded coupled ventricular extrasystoles, ventricular tachycardia, and ventricular fibrillation before and during repeated Stokes-Adams attacks in a patient with complete A-V block, auricular fibrillation, and bundle branch block. Four years later, Levine and Matton¹² observed both ventricular fibrillation and asystole lasting five minutes in a patient with Stokes-Adams syndrome. In 1929, Davis and Sprague¹³ found 13 recorded cases of ventricular fibrillation in man, of which five cases were in association with complete A-V block. They recognized that ventricular fibrillation might be an underlying mechanism in the syncope of Stokes-Adams syndrome, but felt that its frequency could not be estimated because of the paucity of recorded cases. Schwartz¹⁴ in 1932 observed syncopal seizures resulting from ventricular fibrillation in a patient with complete A-V block. Later the same year Schwartz and Jezer¹⁵ reported another similar case. In 1940 Bellet and McMillan,¹⁶ in their textbook description, noted the occurrence of both ventricular tachycardia and ventricular asystole in a case of Stokes-Adams syndrome.

There are now 20 cases on record in which both ventricular arrhythmias and ventricular standstill have been shown to occur during Adams-Stokes syncope. As a result of these observations, and particularly as a result of the clear statement of the problem by Parkinson, Papp and Evan, it is widely though not completely realized that the determination of the mechanism

responsible for syncope in each case is essential to the intelligent treatment of the syndrome. The following case illustrates the problem in therapy presented by the recognition of the several causes of the syncopal attacks. The case also illustrates graphically the varying mechanisms that can occur in Stokes-Adams syncope.

CASE REPORT

An 82 year old man was admitted to the medical wards of the Philadelphia General Hospital on August 20, 1947, with a history of having been awakened from sleep by severe chills, marked tremor and vomiting. He was able to call out to his

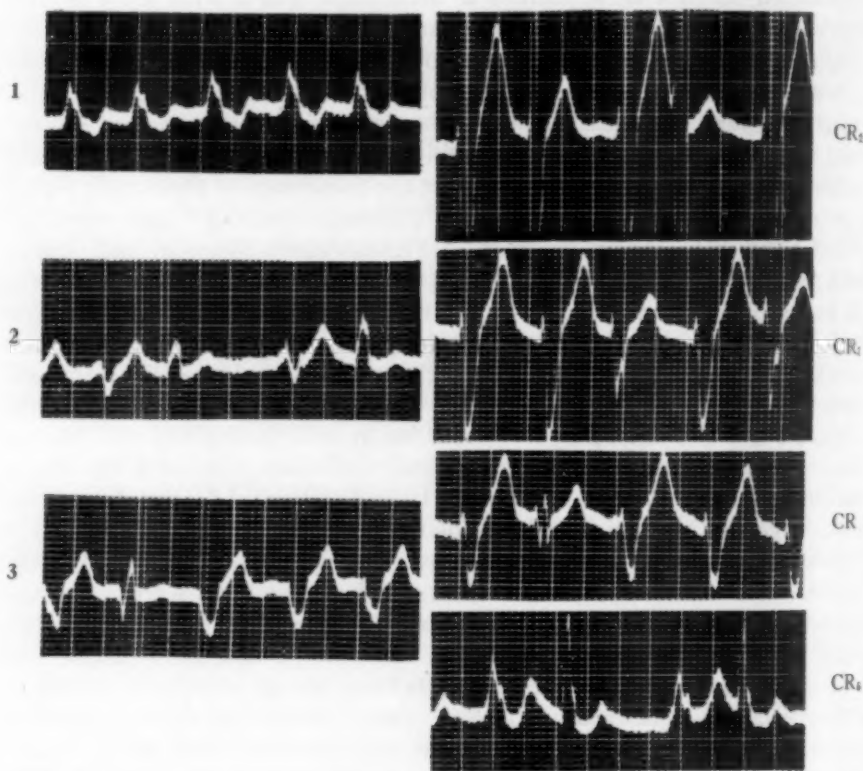


FIG. 1. Electrocardiogram taken at 2:00 a.m. on August 20, 1947, showing auricular fibrillation, bundle branch block, and many extrasystoles. Note QRS complexes of normal width in extrasystoles in Lead III and CR₄.

wife, and then lost consciousness and remained unconscious until shortly after his admission to the hospital about one-half hour later. At the time of the first examination he was in no particular distress. There had been no chest pain, but he complained of some discomfort in his right arm and a "weak spot" in the left upper quadrant of his abdomen. There was no previous history of similar episodes, and except for an attack of exertional dyspnea three months previously, for which he

received what appears to have been placebo therapy, the remainder of the history gave no suggestive evidence of cardiovascular disease.

On admission, his temperature was 100.8° F., apex rate 120 per minute, respiratory rate 24 per minute, and blood pressure 102 mm. Hg systolic and 80 mm. diastolic. The rhythm was very irregular. Although the second sound was clear at all areas, the first sound was faint and indistinct. Reduplication of the second sound was noted. The heart was not enlarged and there were no murmurs or thrills. The peripheral pulse was 112 per minute and irregular. The peripheral vessels were moderately sclerotic. The remainder of the physical examination was not remarkable, and there were no signs of cardiac decompensation.

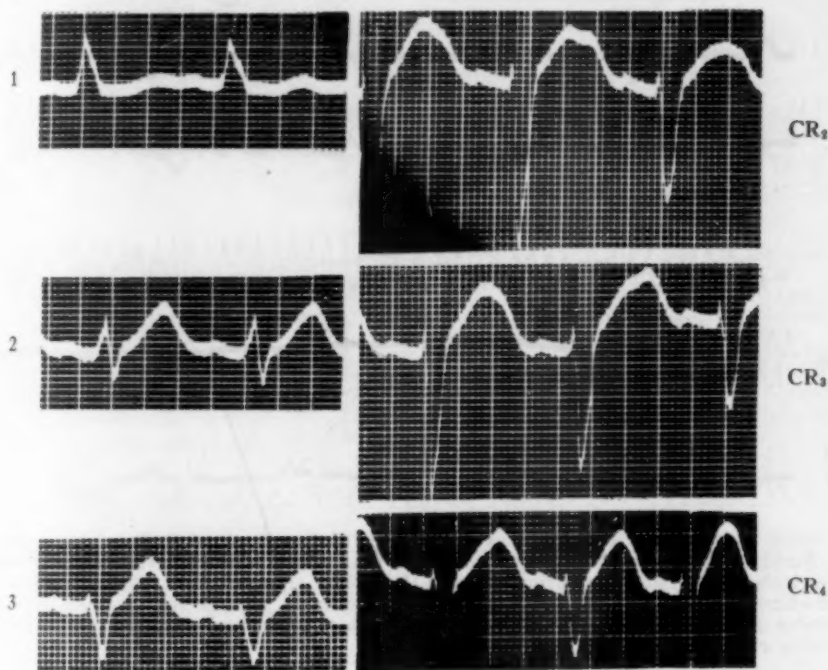


FIG. 2. Tracing taken at 7:30 a.m. on August 20, 1947, showing normal sinus rhythm with prolonged P-R intervals, prolonged Q-T intervals, and blunted T waves. Bundle branch block is still present.

The clinical impression was myocardial infarction, and an electrocardiogram was taken at 2:00 a.m., shortly after admission. This tracing (figure 1) showed auricular fibrillation with a ventricular rate of 120 per minute, bundle branch block, and many extrasystoles. It is interesting to note that some of the extrasystoles have QRS complexes of normal width. There was no evidence of acute myocardial infarction in the tracing. Digitalis was withheld because (1) there were no signs of failure, (2) the ventricular rate was only moderately rapid despite the auricular fibrillation, and (3) a myocardial infarction was suspected. Because of the extrasystoles and the threat of ventricular tachycardia, quinidine was given. Six grains were given at once and six grains six hours later. At 7:30 a.m. on August 21, an electrocardiogram (figure 2) showed restoration of normal sinus rhythm with rounding of the T waves, and prolonged P-R and Q-T intervals. During the night the pulse range had been from 80 to 100 per minute.

At 10:00 a.m. on August 21, the patient was found to be trembling and was thought by the nurse to be having a chill. Immediately after this observation he developed convulsive movements of his extremities, became cyanotic, and was incontinent of urine and feces. Convulsive episodes continued until the time of death at 1:00 p.m., and he never fully regained consciousness. Intracardiac adrenalin was administered terminally without effect.

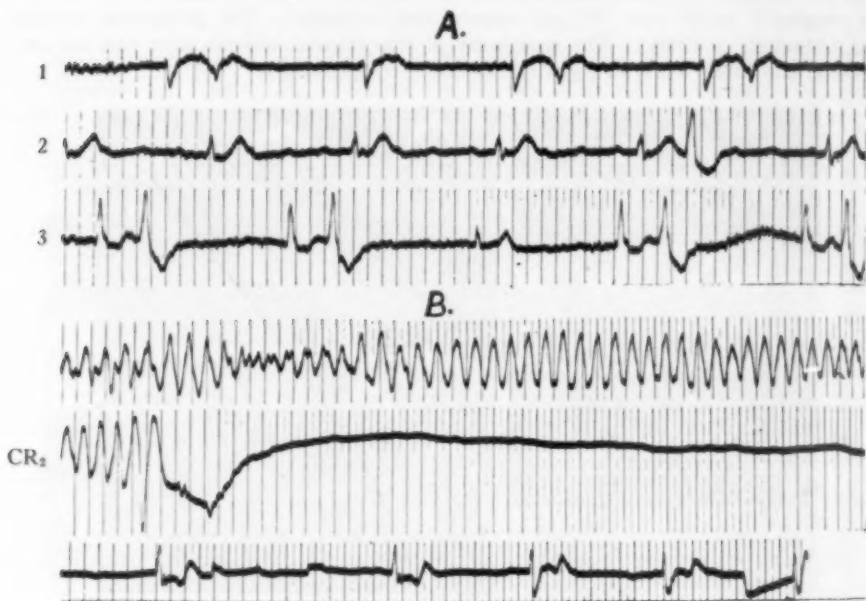


FIG. 3. Beginning of continuous EKG taken during attack of Stokes-Adams syncope. A. Standard limb leads showing complete A-V heart block with the development of coupled ventricular extrasystoles appearing in Leads II and III. B. Continuous tracing taken on CR₂ immediately following, showing prefibrillary ventricular tachycardia, merging into ventricular asystole with continuation of auricular beats, and reappearance of the idioventricular rhythm in the third strip.

A series of electrocardiograms was taken during this prolonged syncopal attack. The standard limb leads (figure 3A) show complete A-V heart block with an idioventricular rate of 30 per minute, and the development of coupled ventricular extrasystoles. As the leads were changed to record CR₂, a rapid arrhythmia developed. A continuous tracing of this lead (figure 3B) shows this to be a paroxysm of prefibrillary ventricular tachycardia (ventricular flutter) with a rate of 300 per minute, during which there are a number of cycles of ventricular fibrillation, followed by a period of ventricular asystole during which the auricles continue to beat at a rate of 70 per minute. The ventricular beat is slowly resumed toward the end of the strip, and complete A-V block is again present. Lead CR₂ (figure 4A) shows once again the complete A-V heart block, now with a ventricular rate of 33 per minute, with coupled ventricular extrasystoles developing in the second strip. Lead CR₂ (figure 4B) shows a run of bizarre ventricular complexes followed by a period of ventricular asystole, and CR₂ (figure 4C) shows in succession complete heart block, a short run of ventricular tachycardia with very abnormal ventricular complexes, and a period of ventricular asystole. Finally a prolonged period of ventricular tachycardia oc-

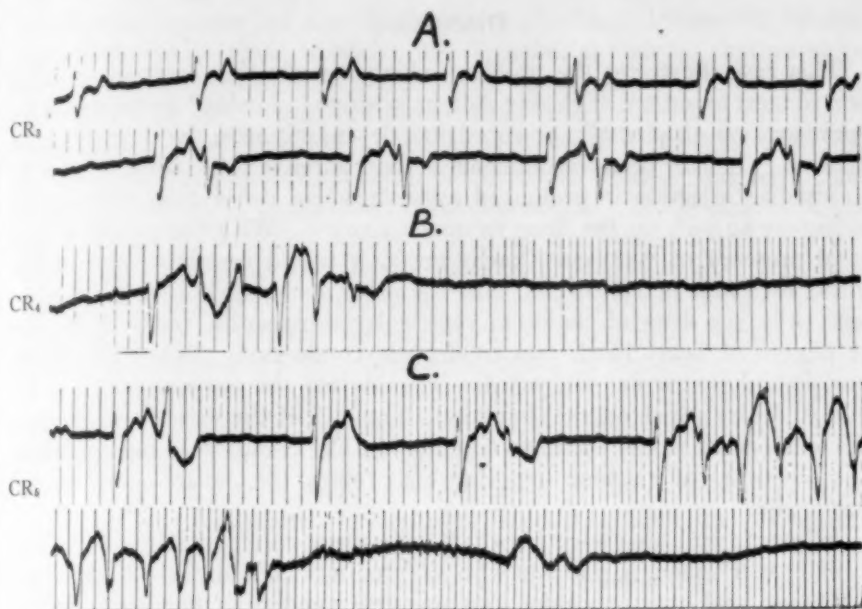


FIG. 4. Continuation of EKG taken during attack of Stokes-Adams syncope. A. Lead CR_3 showing complete A-V heart block with the development of coupled ventricular extrasystoles in the second strip. B. Short run of ventricular tachycardia in lead CR_4 , followed by period of ventricular asystole. C. Complete heart block, ventricular tachycardia, and ventricular asystole occurring in succession in continuous tracing of CR_6 .

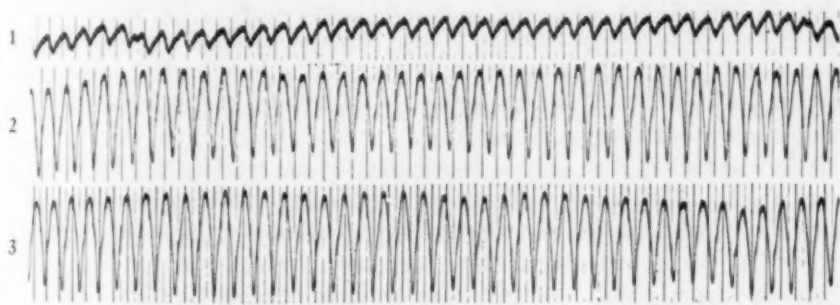


FIG. 5. Continuation of EKG taken during attack of Stokes-Adams syncope. Standard limb leads showing the run of prefibrillatory ventricular tachycardia (ventricular flutter) which continued until death.

currer (figure 5) which continued for a period of about 10 minutes. Abrupt cessation of this mechanism with complete standstill of the galvanometer string occurred at a moment when the machine had been stopped for rewinding, and only a feeble ventricular response could be produced with the intracardiac injection of adrenalin.

Necropsy revealed moderate dilatation of the heart but no definite cardiac enlargement. There were small areas of fibrosis, but no gross evidence of any acute myocardial process was visible. Except for sclerotic changes at the base of the aortic valve and septum there were no findings of significance in the rest of the examination, including the microscopic study.

DISCUSSION

This case illustrates the problem which the clinician faces when called upon to treat an attack of Stokes-Adams syncope. Levine⁴ recommends the administration of adrenalin or ephedrine, depending upon the urgency of the situation. It has been recommended that adrenalin be administered by intracardiac injection in prolonged asystole where the circulation might be inadequate to pick up the drug from the tissues. With the potentiality or actual presence of ventricular tachycardia, it would certainly seem unwise to use adrenalin or ephedrine. On the other hand, quinidine, believed by some to be the drug of choice in ventricular tachycardia, tends to increase the degree of heart block and to depress conduction. When ventricular asystole and ventricular tachycardia occur during the same attack, it is difficult to decide which course to follow. Since all of the various mechanisms which can occur would sound to auscultation like cessation of the heart beat, it is obviously of extreme importance to follow the patient electrocardiographically.

Schwartz and his co-workers^{17, 18} have made careful studies of the pre-fibrillary mechanism in patients who suffered transient attacks of ventricular fibrillation, and have concluded that transient ventricular fibrillation in man has never been observed to be ushered in abruptly without premonitory electrocardiographic signs, even though these may have lasted only a few seconds. The electrocardiographic signs consist of changes in the basic ventricular rate, the development of "initial" premature beats of the ventricles, at first singly and then in groups, and, finally, the appearance of short groups of fibrillary waves. These changes produce varying intervals between basic ventricular complexes of the A-V nodal rhythm, and produce irregular pulse pauses which can be recognized clinically but more accurately identified electrocardiographically.

It is interesting that only a few cycles in our tracing can be identified as ventricular fibrillation. Many authors have erroneously described as ventricular fibrillation what is more properly called "prefibrillary ventricular tachycardia," or ventricular flutter (although the resemblance to flutter is only a superficial one). In the series of cases reviewed by Parkinson and his co-workers,⁹ only a few of the cases showed what was undoubtedly true ventricular fibrillation. This serves to emphasize that the distinction between these arrhythmias is of academic interest only, since it has been shown repeatedly that the ventricular tachycardia alone is capable of producing the clinical syndrome of syncope and convulsions.

The possible relationship of quinidine to the development of ventricular extrasystolic rhythms has aroused the interest of many investigators. Lewis and his co-workers¹⁹ studied the action of quinidine upon the dog's heart with particular reference to the action on circus movements in the auricles. They concluded that it had a dual action: lengthening the refractory period

which tends to close the gap of responsive muscle, and lowering the rate of conduction which tends to widen it. Whether the circus rhythm stops or is perpetuated depends upon which action predominates. The same workers,²⁰ in a later paper, described ectopic beats under quinidine, and attributed them not to hyperexcitability, such as is thought to produce most extrasystoles, but to a re-entry phenomenon associated in some way with changes in muscle excitability in the direction of depression. In the cases of paroxysmal ventricular fibrillation described by Kerr and Bender¹¹ and cited above, the authors attributed the development of this arrhythmia to quinidine. Coupled ventricular extrasystoles were produced by only 0.4 gm. of quinidine; attacks of ventricular tachycardia and, in one case, ventricular fibrillation also developed under quinidine therapy. When first seen, the patient of Kerr and Bender had auricular fibrillation, complete A-V block and bundle branch block. They too attributed the development of ventricular extrasystoles and tachycardia to changes in refractory period such that re-entry of the excitation wave upon pathways already traveled is brought about. When fibrillation is present a sufficient lengthening of the refractory period, by preventing re-entry, will bring the underlying circus movement to an end. However, given in smaller doses, quinidine does not necessarily tend to ward off fibrillation, but may indeed cause it. The case reported by Davis and Sprague¹² was receiving both digitalis and quinidine, either or both of which, they concluded, might depress conducting tissues enough to permit ventricular circus rhythms in patients with A-V block and bundle branch block.

Levine²¹ tried to establish the value of quinidine in the prevention of ventricular fibrillation. He found that intravenous doses of 5 to 10 mg. per kilogram of body weight would, in the cat, definitely inhibit the facility with which ventricular fibrillation could be produced by faradic stimulation. Blumenthal and Oppenheimer²² found that quinidine would prevent ventricular fibrillation induced by barium chloride perfusion. Dock²³ was able to prevent syncopal attacks due to ventricular fibrillation with quinidine, but Escamilla²⁴ was unable to confirm this estimate of its clinical value in his case.

Schwartz and Jezer²⁵ pointed out that such animal experimentation, where the fibrillation was produced by timed electrical stimuli, was not applicable to fibrillation in man, and that the prophylactic use of the drug was based on meager clinical experience and hypothesis. They were able to produce prefibrillatory ventricular tachycardia or transient periods of ventricular fibrillation within one to nine minutes of the intravenous injection of quinidine (gr. 1 3/4) or quinine (gr. 1/3) in patients with complete A-V heart block who were subject to transient spontaneous seizures of ventricular fibrillation.

Barium chloride has been used in the prevention of ventricular fibrillation. Parsonnet and Hyman²⁶ found it ineffective, and indeed Blumenthal and

Oppenheimer²² used it as the agent for inducing ventricular fibrillation experimentally.

It seems reasonable to assume that in our patient the syncopal attack preceding admission to the hospital was similar in nature to the one which we observed and followed. Whether the second and fatal episode could have been prevented by the use of ephedrine or adrenalin is in the realm of speculation. Certainly the exhibition of quinidine in dosage sufficient, in this patient, to restore normal sinus rhythm and produce marked quinidine effect in the electrocardiogram did not prevent the development of ventricular tachycardia, and may even have favored it.

Shnur⁸ found that adrenalin was more effective than quinidine in terminating an attack in a single case, and Levine¹² reported recovery following intracardiac adrenalin, but certainly the demonstration of ventricular tachycardia during the syncopal attack would appear to indicate that caution is necessary in the use of sympathomimetic drugs in the management of complete heart block with Stokes-Adams syndrome.

SUMMARY

The underlying cardiac mechanism in Stokes-Adams syncope has recently been redefined. In addition to ventricular asystole, generally accepted to be the principal mechanism, ventricular tachycardia, ventricular fibrillation, or any combination of the three may occur during the attack. The recognition of these varying mechanisms is important, since the treatment of ventricular extrasystolic rhythms and ventricular standstill is quite different. The electrocardiogram should be employed to identify the mechanism present in each case before treatment can be planned intelligently. The use of quinidine in preventing ventricular arrhythmias has been questioned; there is some evidence to indicate that this drug may be responsible for the production of ventricular circus rhythms. A case in which both extrasystolic disturbances and ventricular asystole were present is reported and the literature is reviewed.

The authors wish to express their appreciation to Dr. Harrison Flippin, Visiting Physician, Philadelphia General Hospital, for permission to report this case.

BIBLIOGRAPHY

1. Morgagni, J. B.: The seats and causes of disease (translated by Benjamin Alexander, M.D.) V.I., 1769, London, p. 192. Cited by: Major, R. H.: Classic descriptions of disease, 1939, Charles C. Thomas, Baltimore, p. 335.
2. Adams, R.: Cases of disease of the heart accompanied with pathological observations, Dublin Hospital Rep. 4: 396, 1827. Cited by Major, R.: Classic descriptions of disease, 1939, Charles C. Thomas, Baltimore, p. 335.
3. Stokes, W.: Observations on some cases of permanently slow pulse, Dublin Quart. J. M. Sc. 2: 73, 1846. Cited by Major, R.: Classic descriptions of disease, 1939, Charles C. Thomas, Baltimore, p. 355.

4. Levine, S. A.: Clinical heart disease, Ed. 3, 1945, W. B. Saunders Co., Philadelphia, p. 206.
5. White, P. D.: Heart disease, Ed. 3, 1946, Macmillan Company, New York, p. 931.
6. Parkinson, J., Papp, C., and Evan, W.: The electrocardiogram of the Stokes-Adams attack, *Brit. Heart J.* 3: 171, 1946.
7. Parsonnet, A. E., Berstein, A., and Klosk, E.: Ventricular fibrillation with special reference to the Morgagni-Adams-Stokes syndrome: report of an unusual case, *Am. Heart J.* 31: 769, 1946.
8. Schnur, S.: Newer concept of Stokes-Adams syndrome, *Am. Heart J.* 35: 298, 1948.
9. Lewis, T.: The mechanism and graphic registration of the heart beat, Ed. 3, 1925, Shaw and Sons, London, Ltd.
10. Starling, H. J.: Heart block influenced by the vagus, *Heart* 8: 31, 1921.
11. Kerr, W. J., and Bender, W. L.: Paroxysmal ventricular fibrillation with cardiac recovery in a case of auricular fibrillation and complete heart block while under quinidine therapy, *Heart* 9: 269, 1922.
12. Levine, S. A., and Matton, M.: Observations on a case of Adams-Stokes syndrome showing ventricular fibrillation and asystole lasting five minutes with recovery following intracardiac injection of adrenalin, *Heart* 12: 272, 1926.
13. Davis, D., and Sprague, B.: Ventricular fibrillation: its relation to heart block, *Am. Heart J.* 4: 559, 1929.
14. Schwartz, S. P.: Transient ventricular fibrillation, *Arch. Int. Med.* 49: 282, 1932.
15. Schwartz, S. P., and Jezer, A.: Transient ventricular fibrillation, *Arch. Int. Med.* 1: 450, 1932.
16. Bellet, S., and McMillan, T. M.: Chapter xxviii, *Electrocardiography in Stroud, W. D.: The diagnosis and treatment of cardiovascular disease, 1940, F. A. Davis Co., Philadelphia, p. 657.*
17. Schwartz, S. P.: Studies on transient ventricular fibrillation. III. The prefibrillatory mechanism during established A-V dissociation, *Am. J. M. Sc.* 192: 153, 1936.
18. Schwartz, S. P., Orloff, J., and Fox, C.: Transient ventricular fibrillation. I. The prefibrillatory period during established A-V dissociation with a note on the phonocardiograms obtained at such times, *Am. Heart J.* 37: 21, 1949.
19. Lewis, T., Drury, A. N., Iliescu, C. C., and Wedd, A. M.: Observations relating to the action of quinidine on the dog's heart; with special reference to the action in clinical fibrillation of the auricles, *Heart* 9: 55, 1921.
20. Lewis, T., Drury, A. N., Wedd, A. M., and Iliescu, C. C.: Observations of the action of certain drugs upon fibrillation of the auricles, *Heart* 9: 207, 1922.
21. Levine, H. D.: Effect of quinidine sulfate in inhibiting ventricular fibrillation, *Arch. Int. Med.* 49: 808, 1932.
22. Blumenthal, B., and Oppenheimer, E. T.: Method for the study of ventricular fibrillation, *Am. Heart J.* 18: 363, 1939.
23. Dock, W.: Transient ventricular fibrillation as a cause of syncope and its prevention by quinidine sulfate, *Am. Heart J.* 4: 709, 1929.
24. Escamilla, R. F.: Report of a case of paroxysmal ventricular fibrillation in relation to quinidine therapy, *Am. Heart J.* 8: 850, 1933.
25. Schwartz, S. P., and Jezer, A.: The action of quinine and quinidine on patients with transient ventricular fibrillation, *Am. Heart J.* 9: 792, 1934.
26. Parsonnet, A. E., and Hyman, A. S.: Barium chloride in the Stokes-Adams syndrome of complete heart block: negative results in eight cases, *Am. J. M. Sc.* 180: 356, 1930.

ISOLATED DISEASE OF THE PULMONARY VALVE AND ARTERY *

By ALBERT L. HYMAN, *London, England*, LOUIS LEVY, II, RICHARD BAGNETTO, NELSON K. ORDWAY, and EDGAR HULL, F.A.C.P.,
New Orleans, Louisiana

THE purpose of the present communication is to present seven cases of organic heart disease in which there is isolated involvement of the pulmonary artery or valve, and to indicate the importance of certain physical signs and laboratory procedures in their diagnosis. Each individual was studied while a patient in Charity Hospital at New Orleans. All but one were encountered within a few months of each other. Three patients are presented as examples of congenital isolated stenosis of the pulmonary valve, two as examples of acquired pulmonary valvulitis, and two as examples of pulmonary artery aneurysm secondary to infection.

CONGENITAL ISOLATED PULMONARY STENOSIS

Congenital isolated pulmonary valvular stenosis is one of the rare forms of congenital heart disease. Greene et al.¹ recently reviewed the 71 reported cases and presented four additional ones.

Dyspnea is commonly present, but cyanosis is slight or absent early in life and, if present, usually makes its appearance as a late manifestation. The characteristic physical sign is a loud systolic murmur at the pulmonic area, frequently associated with a thrill. The pulmonary second sound is decreased in intensity and is not duplicated. Occasionally, as in two of our cases and two of the reported ones, there is an early diastolic pulmonic murmur. When these patients develop congestive failure it is mainly "right-sided," characterized by increased venous pressure, edema, hepatomegaly and ascites.

The circulation time is prolonged. The electrocardiogram is characteristic of right ventricular hypertrophy. Marked hypertrophy of the right ventricle occurs, and there may be tricuspid incompetency with enlargement of the right atrium and superior vena cava, features which may be demonstrated by roentgenographic examination. The roentgenogram also shows abnormal clarity of the lung fields. A delayed emptying time of the right ventricle, together with enlargement of the right atrial and ventricular shadows, should be demonstrable by angiocardiography.

Venous catheterization² reveals similarity in the oxygen contents of blood samples withdrawn from the great veins, right atrium, right ventricle

* Received for publication February 12, 1949.

From the Heart Station of Charity Hospital of Louisiana at New Orleans, and the Departments of Medicine and Pediatrics of Louisiana State University School of Medicine.

and pulmonary artery. The right ventricular pressure, and sometimes the right atrial, are abnormally high, while that of the pulmonary artery is abnormally low.

The oxygen saturation of the systemic arteries is normal; cyanosis, if present, should therefore be referable to considerable venous unsaturation secondary to peripheral stagnation.

The life expectancy of the patient with isolated pulmonary stenosis is considerably reduced. The mean age at death of the 63 cases reviewed by

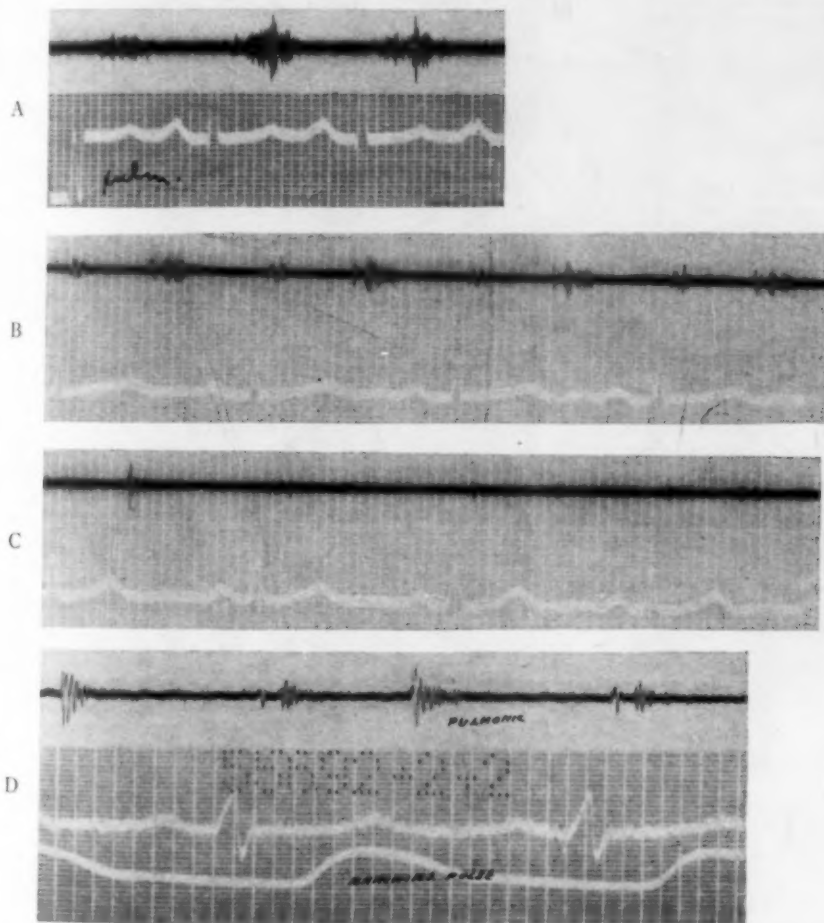


FIG. 1. A. Sound tracing of case 2 shows systolic and diastolic murmurs, with an absence of any murmur in the last two-thirds of diastole. B. Sound tracing of case 4 shows early systolic and diastolic murmurs, with an absence of any murmur in the last two-thirds of systole and diastole. C. Sound tracing of case 6 shows early systolic and diastolic murmurs, with an absence of any murmur in the last two-thirds of systole and diastole. D. Sound tracing of case 7 shows an early systolic and decrescendo diastolic murmur.

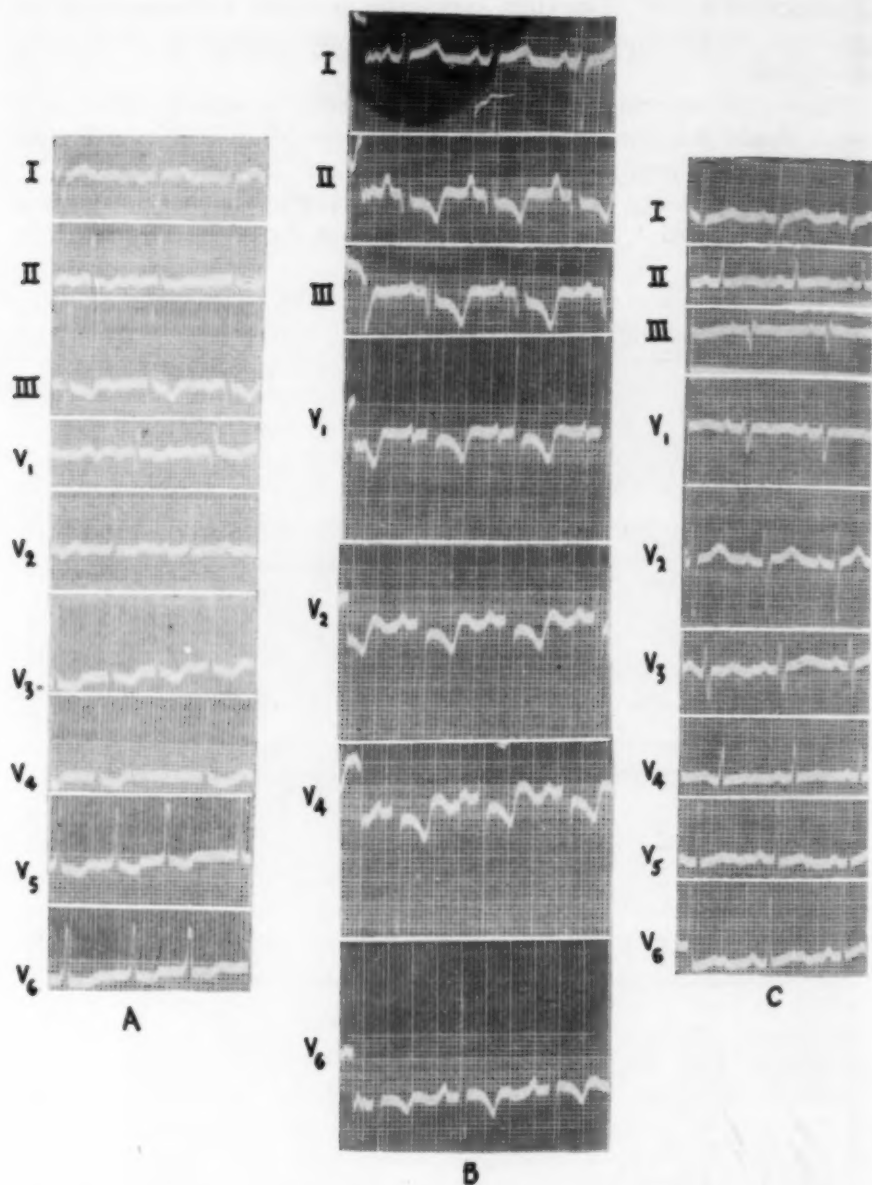


FIG. 2. A. Cardiogram of case 2 shows right axis deviation with a terminal R in V_1 (without any widening of the QRS complexes) compatible with right-ventricular hypertrophy. B. Cardiogram in case 3 shows a marked right axis deviation with a high R in V_1 compatible with right ventricular enlargement. C. Cardiogram of case 4 shows notching of T- V_4 , 5, 6.

Greene was 26 years.¹ The longest reported survival is 75 years, while the shortest is five months.

Congenital pulmonary stenosis may be of the valve proper or of the infundibulum of the right ventricle. Two cases to be reported are believed to represent the former type and one the latter.

CASE REPORTS

*Case 1.** An 18 month old white male was admitted to Charity Hospital on June 23, 1948, because of bilateral pedal edema of five days' duration. There had been no cyanosis or dyspnea in the neonatal period. From the age of four months

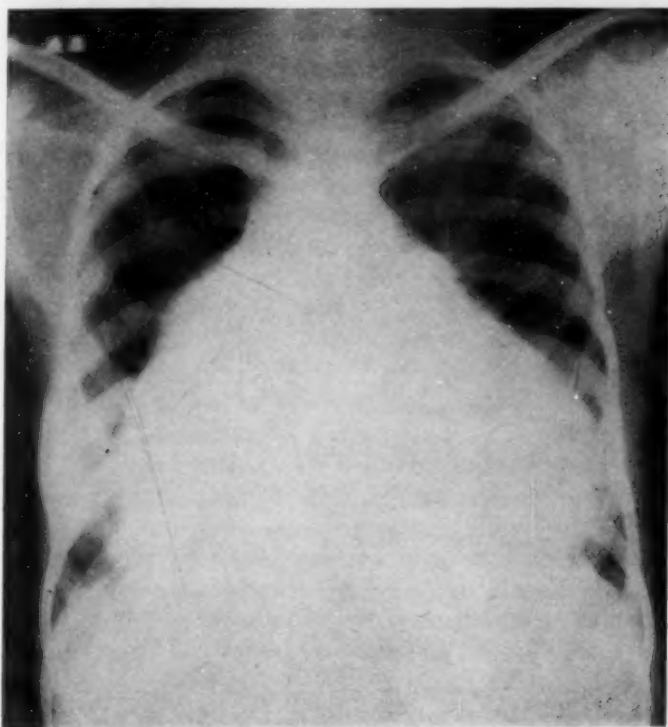


FIG. 3A. (Case 2.) P-A view: marked enlargement to the right and left with a double contour on the right border (right atrium and ventricle), prominence of the superior vena cava, a convexity in the region where the pulmonary artery is normally seen, and abnormally clear lung fields.

the infant had had four brief periods of unconsciousness. Physical examination revealed blood pressure of 128 mm. Hg systolic and 90 mm. diastolic; pulse 130 per minute; anasarca; heart enlarged to right and left, with gallop rhythm and harsh systolic and diastolic murmurs heard best at the pulmonic area; lungs clear; enlarged pulsating liver.

* This case will be reported in detail in a subsequent paper.

Laboratory findings: red blood cells 4.34 mil. per cu. mm., hemoglobin 12.5 gm. per 100 c.c., white blood cells 9,400-28,700 per cu. mm., with 35 to 40 per cent granulocytes; 2 to 3 plus albuminuria, hyaline and fine granular casts present; blood urea nitrogen 18 mg. per 100 c.c.; serum protein 4.4 gm. per 100 c.c. with A/G ratio 3/1.4; serum cholesterol 192 mg. per 100 c.c. An electrocardiogram was compatible with right ventricular hypertrophy and right atrial enlargement. Roentgenographic

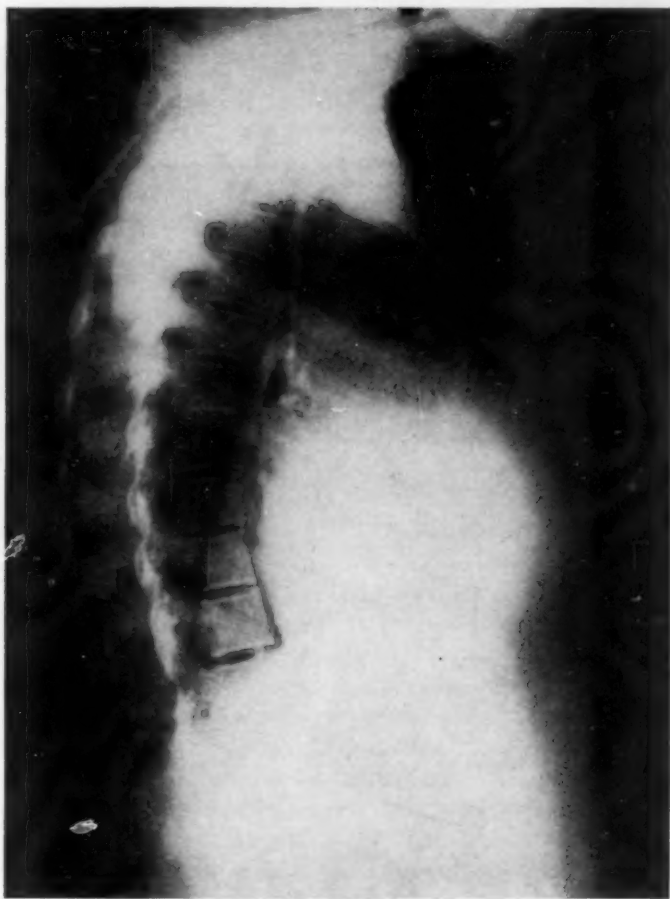


FIG. 3B. Left lateral view, case 2.

and fluoroscopic examination revealed massive enlargement of the cardiac shadow, due mainly to the right ventricle, with prominence of the pulmonary conus and clear lung fields.

Gangrene of the right foot occurred four days prior to death.

Necropsy findings: Marked right atrial and ventricular hypertrophy and dilatation; fused, thickened pulmonary valve cusps, with a central aperture 1 mm. in diameter; relatively enlarged tricuspid valve; gangrene of the right leg and foot; thrombosis of the cerebral vessels.

COMMENT

In case 1 a correct antemortem diagnosis was based on the following considerations: presence of right-sided failure in a noncyanotic child with a loud systolic heart murmur at the pulmonic area, a large right heart, and clear lung fields interpreted as indicating absence of a septal defect.

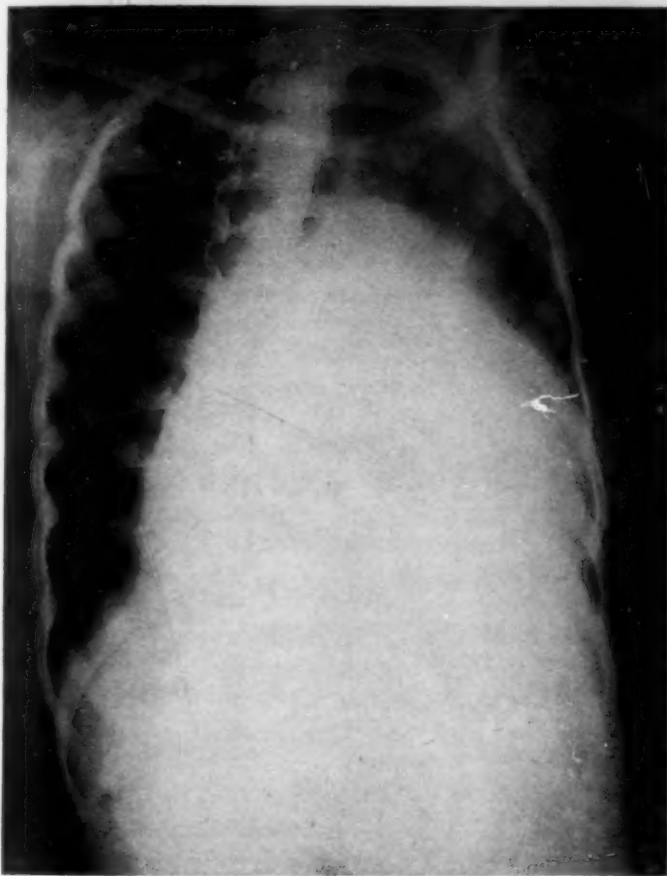


FIG. 3C. Right anterior oblique view, case 2: prominence in the region of the pulmonary conus, with a generalized enlargement posteriorly.

Case 2. A 16 year old colored female was first seen at Charity Hospital on October 31, 1940, at the age of eight years, when she was admitted for tonsillectomy. She had had attacks of dyspnea since birth. Physical examination revealed a loud, harsh, systolic pulmonic murmur. She was apparently well, except for frequent attacks of dyspnea, until January, 1947, when at the age of 14 years she was admitted to Charity Hospital with signs of right-sided cardiac failure, namely, increased venous pressure, ascites, enlarged pulsating liver, and edema of the face and lower extremities. Physical examination revealed, in addition to the above, blood pressure

115 mm. Hg systolic and 90 mm. diastolic; pulse 90 per minute, with total irregularity; cardiac enlargement to the right and left; systolic thrill at the pulmonic area; loud, harsh systolic murmur, and moderately loud diastolic murmur, heard best at the same region (figure 1).

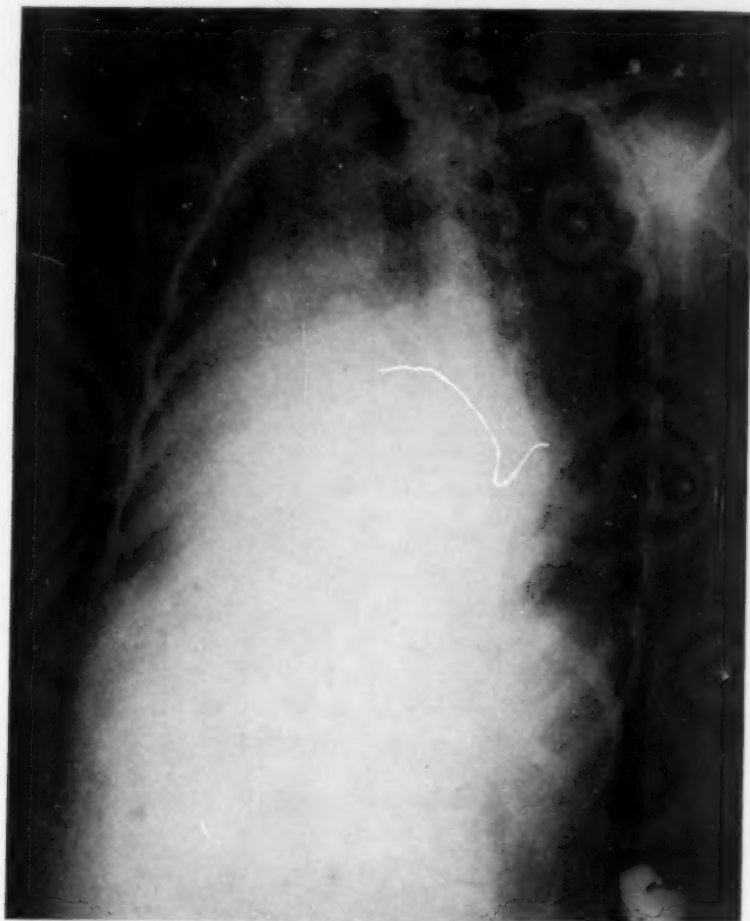


FIG. 3D. Left anterior oblique view, case 2: enlargement of the right ventricle anteriorly, with displacement of the left ventricle posteriorly and fullness of the aortic window.

Laboratory findings: Red blood cells 4.1 mg. per cu. mm., packed cell volume 40 per cent, white blood cells 5,800 per cu. mm. with normal differential; negative urinalysis; electrocardiogram compatible with right ventricular hypertrophy (figure 2). Roentgenologic examination revealed massive right atrial and ventricular enlargement with a prominent pulmonary conus and decreased lung markings (figure 3).

On this admission she responded well to digitalis, mercurial diuretics and a salt-free diet. During the next 18 months she had numerous readmissions for abdominal paracentesis and therapy of right-sided heart failure.

Three cardiac catheterizations and arterial oxygen studies during this period yielded similar results (tables 1, 2). Repeated attempts to pass the catheter into the pulmonary artery were unsuccessful. The mean pressures in the superior vena cava, right atrium and right ventricle, observed with a saline manometer, were similar, and all were elevated above normal. The arterial oxygen saturation was 93 per cent. The arteriovenous oxygen difference was 8 vol. per 100 c.c.

TABLE I

Position of catheter	Case 2		Case 3		Case 4		Case 5		Case 6	
	P*	O ₂ *	P*	O ₂ *	P*	O ₂ *	P*	O ₂ *	P*	O ₂ *
Right pulmonary artery				10.1		6.3	24	10.2	28	12.2
Left pulmonary artery						6.4				
Main pulmonary artery			17	9.9		6.8	25	9.9	28	10.8
Right ventricle conus region	41	7.2		10.0		6.3	21	10.1	23	11.1
Right ventricle mid portion	37	6.0	65	9.4			23	10.0	25	11.0
Right atrium at tricuspid valve				10.9		5.9	11	10.5		
Right atrium mid portion	37	6.7	11	10.0						
Superior vena cava	37	6.7		9.7		6.5		9.6	9	10.7

*P: Mean pressure in mm. mercury, measured from the level of the patients' backs as 0.
 O₂: Oxygen content of whole blood in volumes per 100 c.c. corrected to standard temperature and pressure. Oxygen determinations performed by a modified Roughton-Scholander micromethod.

TABLE II

Procedure	Percentage Saturation*			
	Case 2	Case 3	Case 4	Case 5
Resting, breathing air	93	92	89	89
Resting, breathing 100% O ₂	100	100	100	100
Exercising, breathing air	93	93	92	93

$$* \% \text{ saturation} = \frac{\text{content of HbO}_2}{\text{HbO}_2 \text{ capacity}}$$

Normal range = 91-96%.

COMMENT

In case 2 the diagnosis is based on observations similar to those in case 1. The findings at cardiac catheterization indicate right-sided failure and appear to rule out a left-to-right shunt. The normal arterial oxygen saturation rules out a right-to-left shunt. The diastolic murmur in each patient is believed to represent insufficiency of the stenotic pulmonary valve. In each case the prominence of the conus portion of the right ventricle in the roentgen-ray silhouette is interpreted as consistent with valvular rather than infundibular stenosis. This was demonstrated at post mortem in case 1. The etiology of the lesion in case 2 is speculative, but its congenital nature is suggested by the history of life-long attacks of dyspnea.

Case 3. A colored male was referred to Charity Hospital in 1945 at the age of 9 years because of a murmur discovered on routine school health examination. There was no history of cyanosis or physical or mental retardation. Physical examination at that time revealed a loud, low-pitched systolic murmur heard over the entire precordium and loudest at the third left intercostal space near the sternal border. There was a systolic thrill in the same area. A bulging of the precordial region was noted.

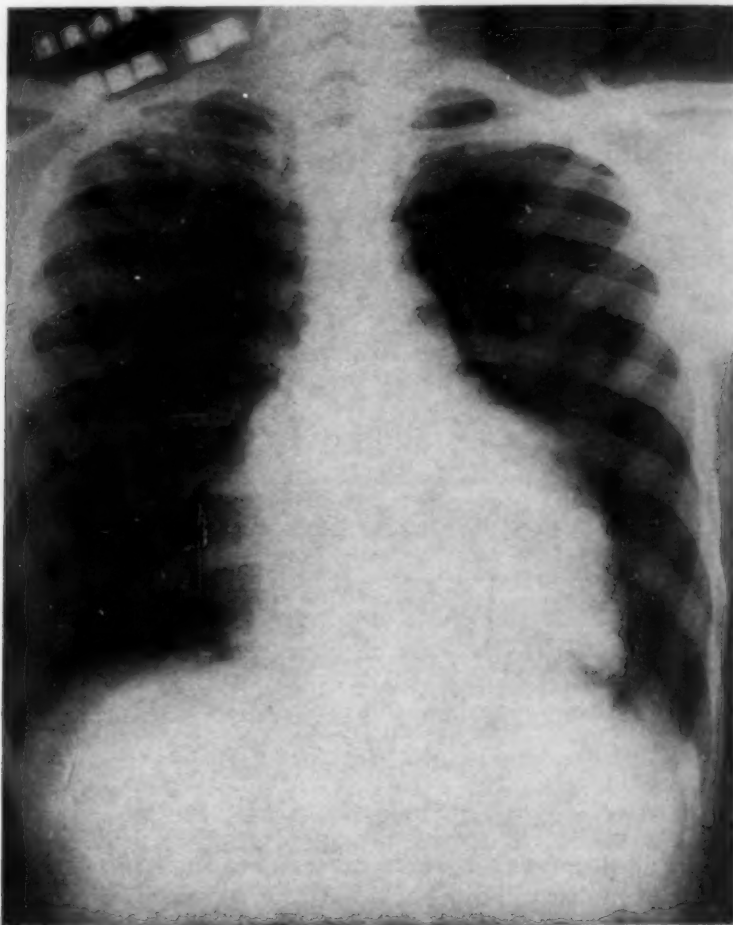


FIG. 4A. P-A view: enlargement of the cardiac shadow to the right and left, with a concavity in the usual pulmonary artery region.

Laboratory examination: 4.7 mg. red blood cells per cu. mm.; 12.2 gm. of hemoglobin; enlargement of the cardiac shadow to the left on P-A roentgenogram of chest; electrocardiogram compatible with right ventricular hypertrophy.

A diagnosis of interventricular septal defect was made, and he was followed in the clinic for the next three years without developing any symptomatology referable to his heart. He was readmitted on December 6, 1948, for a further diagnostic work-

up. At that time examination revealed: blood pressure 100 mm. Hg systolic and 66 mm. diastolic, markedly diminished pulmonary second sound, and a murmur similar to that heard at the first visit. His red blood cell count at the time was 4.76 mg. per cu. mm. Roentgenologic examination revealed, in the P-A views, cardiac enlargement to the right and left, with a concavity in the usual pulmonary artery region

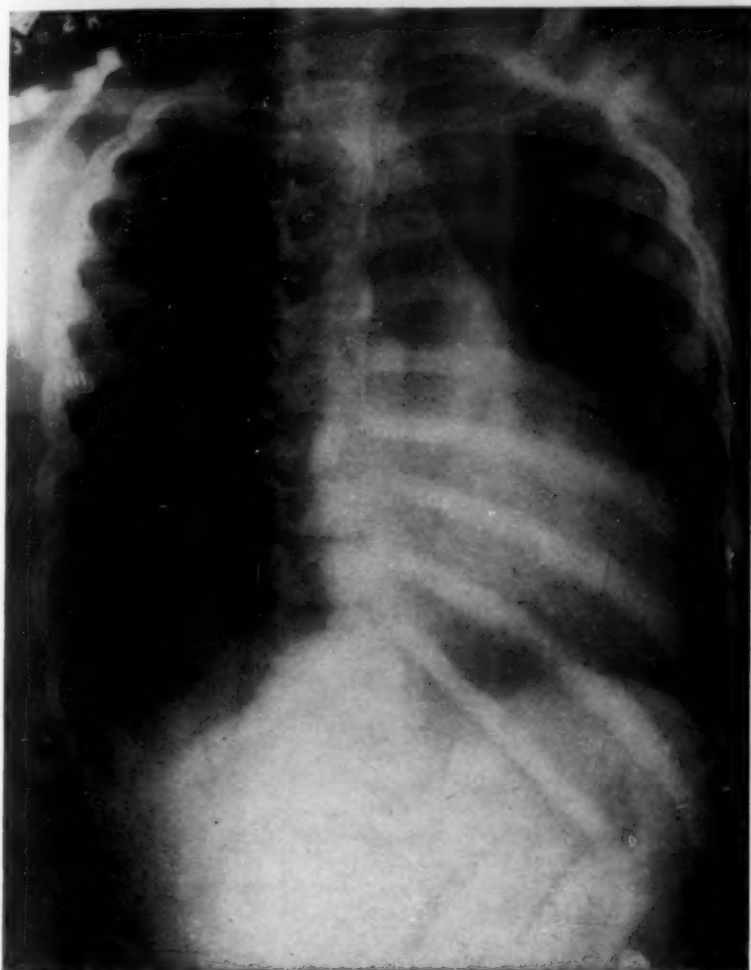


FIG. 4B. Right anterior oblique view: concavity in the usual pulmonary artery area.

and a localized bulging just superior to this area; in the right anterior oblique position, a concavity was seen in the usual pulmonary artery region; in the left anterior oblique position, the right ventricle was seen to be markedly enlarged, displacing the left ventricle posteriorly, and the pulmonary artery filled the aortic window (figure 4). An electrocardiogram revealed extreme right axis deviation with a high R in V_1 , inverted $T_{2,3}$, $V_{2,3,4,5,6}$, and was compatible with right ventricular hypertrophy (figure 2). Angiocardiograms revealed dilatation of the pul-

monary artery (figure 4). Peripheral arterial oxygen studies revealed no abnormalities (table 2). Cardiac catheterization revealed similar oxygen saturation values in the right atrium, right ventricle and pulmonary arteries; a mean right ventricular pressure of 65 mm. Hg, and a pulmonary artery pressure of 17 mm. Hg (figure 5

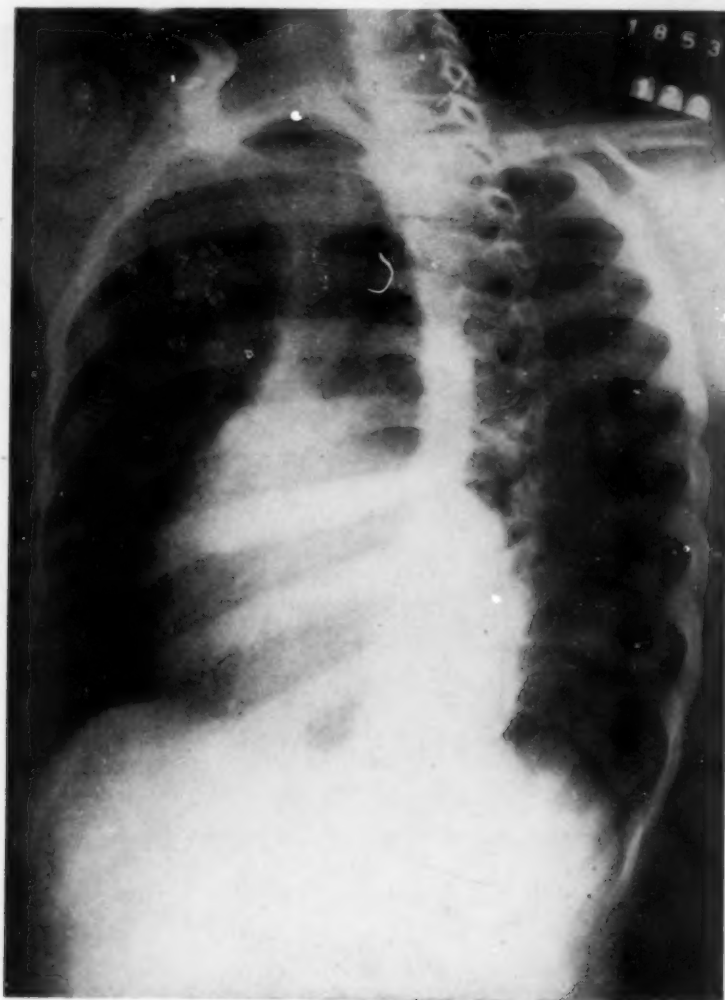


FIG. 4C. Left anterior oblique view: right ventricle markedly enlarged, displacing the left ventricle posteriorly.

and table 1). The A-V oxygen difference was 4.9 vol. per 100 c.c. At the time of catheterization it was difficult to advance a #8 French catheter into the pulmonary artery which, from the position of the catheter, could now be identified as producing the bulge high on the left cardiac border previously noted on roentgenologic examination. The catheter tip was noted to have a diminished amplitude of pulsation in the area of the right ventricle proximal to the pulmonary artery.

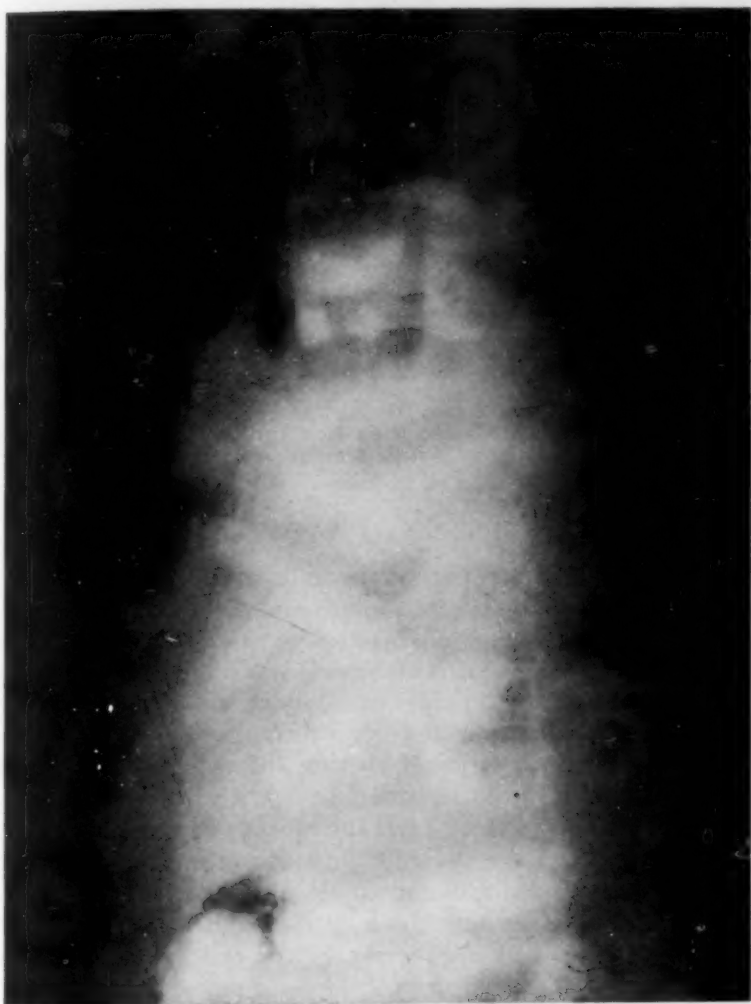


FIG. 4D. Angiocardiogram showing post-stenotic dilatation of pulmonary artery.

COMMENT

In case 3 a diagnosis of isolated pulmonary stenosis was based on the presence of a loud systolic murmur at the pulmonic area, a large right heart, clear lung fields, high right ventricular pressure, relatively low pulmonary artery pressure, and absence of demonstrable shunts as determined by normal arterial oxygen values and venous catheterization. Infundibular rather than valvular stenosis is believed to be present because of the concavity in the region of the normal pulmonary conus, in addition to the course the catheter took during cardiac catheterization. A post-stenotic dilatation was seen on the angiocardiograms.

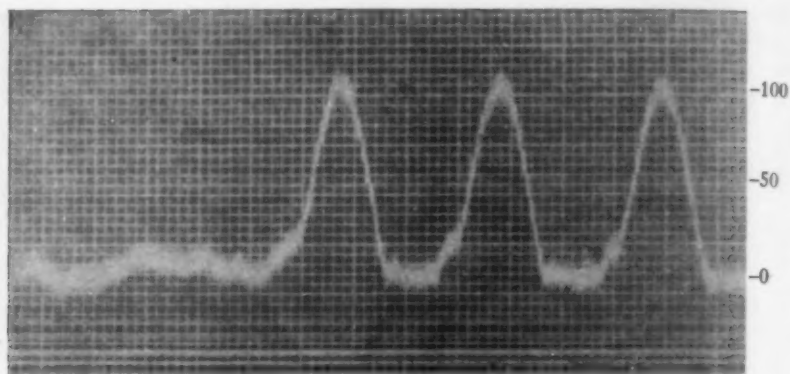


FIG. 5 (Case 3). Pressure tracing obtained with Statham strain gage manometer, during gradual withdrawal of the catheter tip from the pulmonary artery into the right ventricle. Note the marked rise in systolic pressure as the ventricle is entered. No. 8 French catheter.

ACQUIRED PULMONARY VALVULAR DISEASE

Pulmonary valve endocarditis is usually of the acute variety. The pulmonary valve is one of the rarest localizations of subacute bacterial endocarditis.^{4,5} In a recent review of 76 autopsied cases of bacterial endocarditis at Charity Hospital of Louisiana at New Orleans, the lesion was limited to the right side of the heart in six cases (8 per cent), five patients having isolated tricuspid involvement and one patient having isolated pulmonary valve involvement. In a series of 80 cases of endocarditis, Clawson and Bell⁴ found no patients with isolated pulmonary valve involvement. Bacterial infection of the pulmonary valve is frequently engrafted on a congenital lesion. Subacute bacterial endocarditis limited to the right side of the heart is difficult to diagnose due to the usual absence of peripheral bacteremia as a result of filtering out of organisms by the pulmonary vascular bed, the frequent lack of peripheral embolic phenomena and splenomegaly, and the absence of mitral or aortic murmurs. Repeated pulmonary embolism is one of the findings which often arouse the first suspicion of right-sided endocarditis. Cardiac catheterization affords a means of securing blood for culture when right-sided bacterial endocarditis is suspected.

Of the 35 autopsy cases of rheumatic fever analyzed by Clawson and Bell,⁴ only one showed pulmonary valve involvement, and in this case tricuspid, mitral and aortic lesions also occurred. Rheumatic involvement of the pulmonary valve was reported by Lehman⁵ in one case.

Case 4. A 37 year old colored female was admitted on July 24, 1948, with complaints of weight loss, night sweats, cough, anorexia for two weeks, and pedal and facial edema for five days. A chest plate taken two weeks prior to admission showed an area of infiltration at the left base. These were the only positive points in her present illness. She had had granuloma inguinale in 1946 and was treated with

antimony compounds and "looping" with the electrocautery. At that time no cardiac murmurs were heard.

The positive points on physical examination on the present admission were temperature 99.8° F.; blood pressure of 150 mm. Hg systolic and 98 mm. diastolic before exercise, and 160 mm. Hg systolic and 118 mm. diastolic after exercise; slight edema of the ankles; a moderately loud, blowing, high pitched, diastolic murmur at the second left intercostal space near the sternum, and diffuse enlargement of the uterus.

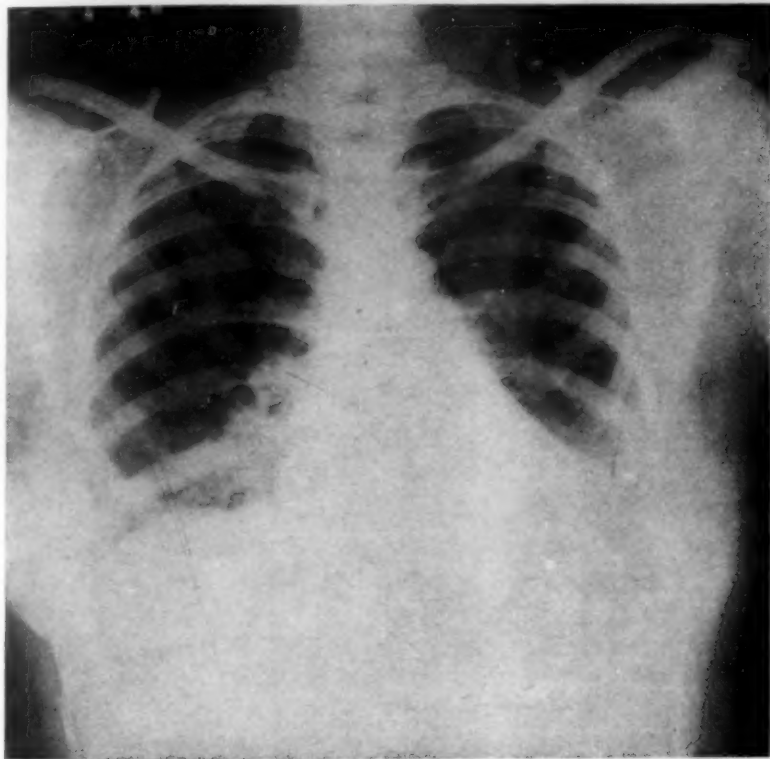


FIG. 6. X-ray of the chest of case 4 reveals cardiac enlargement to the left, with a fullness in the region of the pulmonary artery.

Positive points in initial laboratory work: Red blood cells 2.68 mil. per cu. mm.; reticulocytes 3.2 per cent; hemoglobin 8.7 gm. per 100 c.c.; hematocrit reading 25 per cent; white blood cells 3,500 per cu. mm., with 58 per cent granulocytes, 10 per cent monocytes, toxic granulation of granulocytes; uncorrected sedimentation rate 70 mm. per hour (Wintrobe-Lansberg method); urinalysis 20 to 25 red blood cells per high power field. A P-A chest plate on admission showed clearing of the previous pulmonary lesion and some enlargement of the cardiac shadow (figure 6). Fluoroscopic examination of the heart revealed moderate enlargement of the right ventricle, with a prominent pulmonary artery which showed an increased amplitude of pulsation. A electrocardiogram (figure 2) showed notched T_{V4, 5, 6}.

The edema subsided in three days; however, the patient continued to run a febrile course fluctuating from 98.6° to 103° F. Twenty-one blood cultures were negative. During the week following admission, the pulmonary diastolic murmur increased in intensity and became rougher. A rather rough systolic murmur of moderate in-

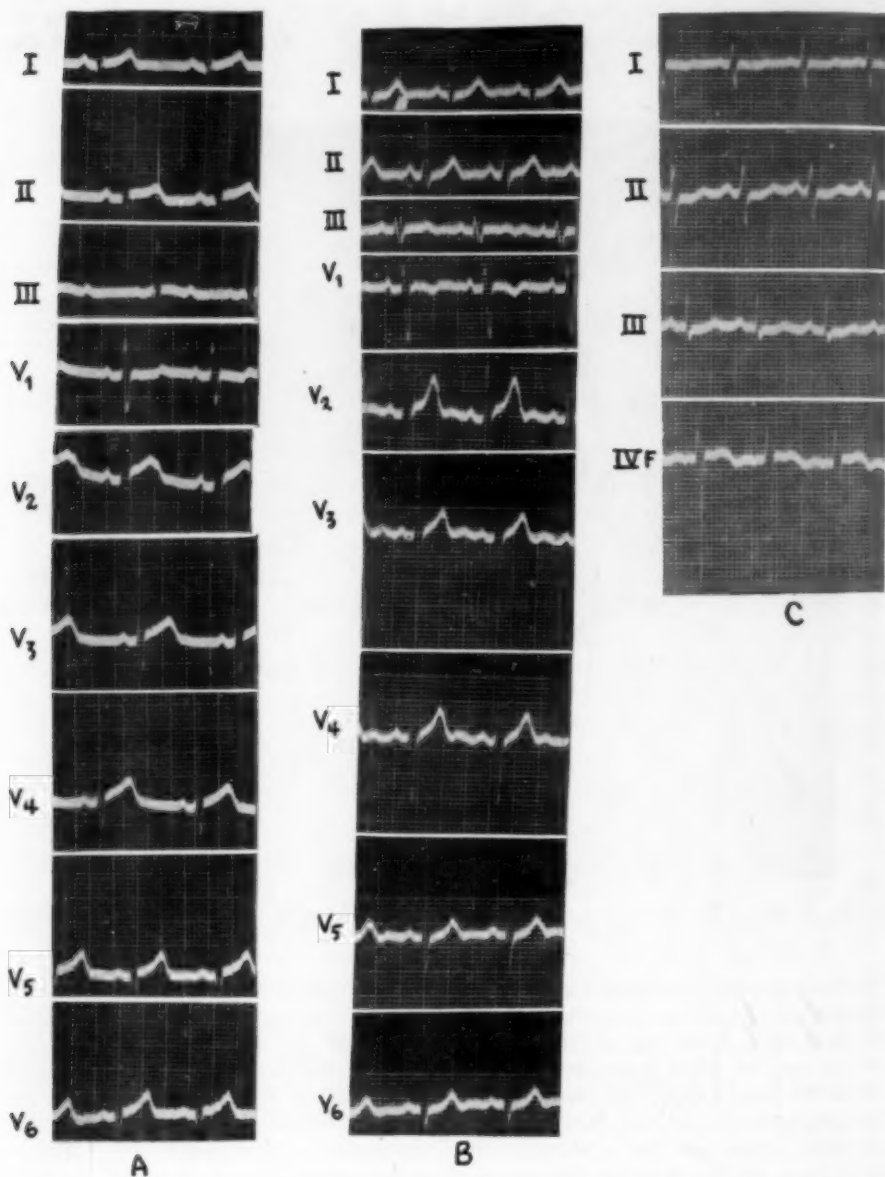


FIG. 7. A. Cardiogram of case 5 is within normal limits. B. Cardiogram of case 6 is within normal limits. C. Cardiogram of case 7 shows slight right axis deviation and a low T₁.

tensity appeared in the same area (figure 1). Arterial puncture revealed an oxygen saturation of 92 per cent, and the blood oxygen findings at cardiac catheterization were normal (tables 1, 2). Blood removed from the pulmonary artery showed on culture nonhemolytic streptococci which were sensitive to penicillin at a level of 0.5 units/c.c. The patient received 1,200,000 units of penicillin intramuscularly for two months of continuous therapy. She became afebrile 36 hours after penicillin was started and remained so. During this period she had an emergency operation for a twisted ovarian cyst.

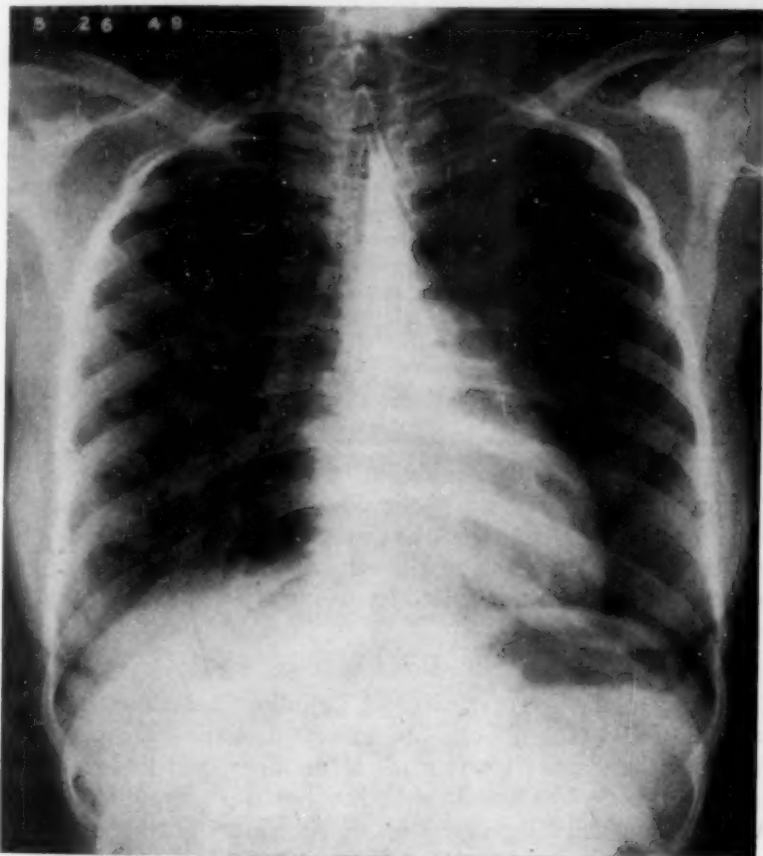


FIG. 8. X-ray of the chest in case 5 reveals a prominence of the pulmonary artery.

COMMENT

In case 4 the febrile course, with possible pulmonary embolization, together with the appearance of systolic and diastolic murmurs of changing intensity and character at the pulmonary valve area, without signs of aortic insufficiency, suggested the diagnosis of bacterial endocarditis of the pulmonic valve. By means of catheterization, the diagnosis is believed to have been confirmed through isolation of an organism from the pulmonary arterial

blood. At the same time, patency of a ductus arteriosus was ruled out. The prompt response to penicillin lends further support to the diagnosis of bacterial endocarditis.

Case 5. A 20 year old colored female was admitted on May 14, 1948, with the chief complaint of "sore throat and fever" for the previous three weeks. After the first two weeks of illness, she developed a migrating polyarthritis which involved her right and left carpal, interphalangeal and coxal joints. The past history was noncontributory.

Positive points on physical examination were a temperature of 99.4° F.; pulse 88 per minute; respiration 22 per minute; blood pressure 122 mm. Hg systolic and 80 mm. diastolic; presence of an acute pharyngitis; multiple tender joints; a loud, blowing, short, high pitched systolic murmur, and a blowing, high pitched, decrescendo diastolic murmur of lesser intensity, both localized to the second left intercostal space near the sternal margin.

Positive laboratory findings: Hematocrit reading 38 per cent, uncorrected sedimentation rate 52 mm. per hour, white blood cells 12,000, with 82 per cent polymorphonuclears, 2 per cent eosinophils, 1 per cent basophils, 3 per cent monocytes, and 12 per cent lymphocytes. Electrocardiogram was within normal limits (figure 7). Fluoroscopic and roentgen-ray examination of the heart revealed prominence of the pulmonary artery, with increase in the amplitude of pulsation and fullness of the aortic window (figure 8). Cardiac catheterization studies revealed no abnormalities, and the arterial oxygen saturation was 93 per cent (tables 1, 2).

COMMENT

A diagnosis of rheumatic infection of the pulmonary valve was made in case 5 on the basis of murmurs believed to indicate pulmonary insufficiency and possibly stenosis, detected in the course of an illness clinically typical of rheumatic fever. There was no clinical evidence of mitral lesion or heart failure, conditions which might lead to pulmonary incompetency.

ANEURYSM OF THE PULMONARY ARTERY

According to the recent review of Deterling and Clagett,⁶ there have been a total of 198 reported cases of aneurysm of the pulmonary artery, in 147 of which the diagnosis was made at necropsy, and in 51 of which the diagnosis was made by clinical methods. Syphilis played a rôle in 39 per cent of Deterling and Clagett's series of pulmonary aneurysms; four cases were due to mycotic involvement. Most pulmonary artery aneurysms are on a congenital basis. The main trunk is usually the primary site of involvement, and the left branch is more frequently involved than the right. The two cases we are reporting are examples of pulmonary artery aneurysms due to intrinsic disease of the vessel wall, one the result of syphilitic and the other of tuberculous involvement. In both cases, angiocardiograms helped to establish the diagnosis and ruled out aortic aneurysm.

Case 6. A 32 year old colored male was admitted to Charity Hospital on March 25, 1948, with a history of cough, hoarseness, fever, night sweats, and repeated episodes of hemolysis for three months. Physical examination revealed: temperature

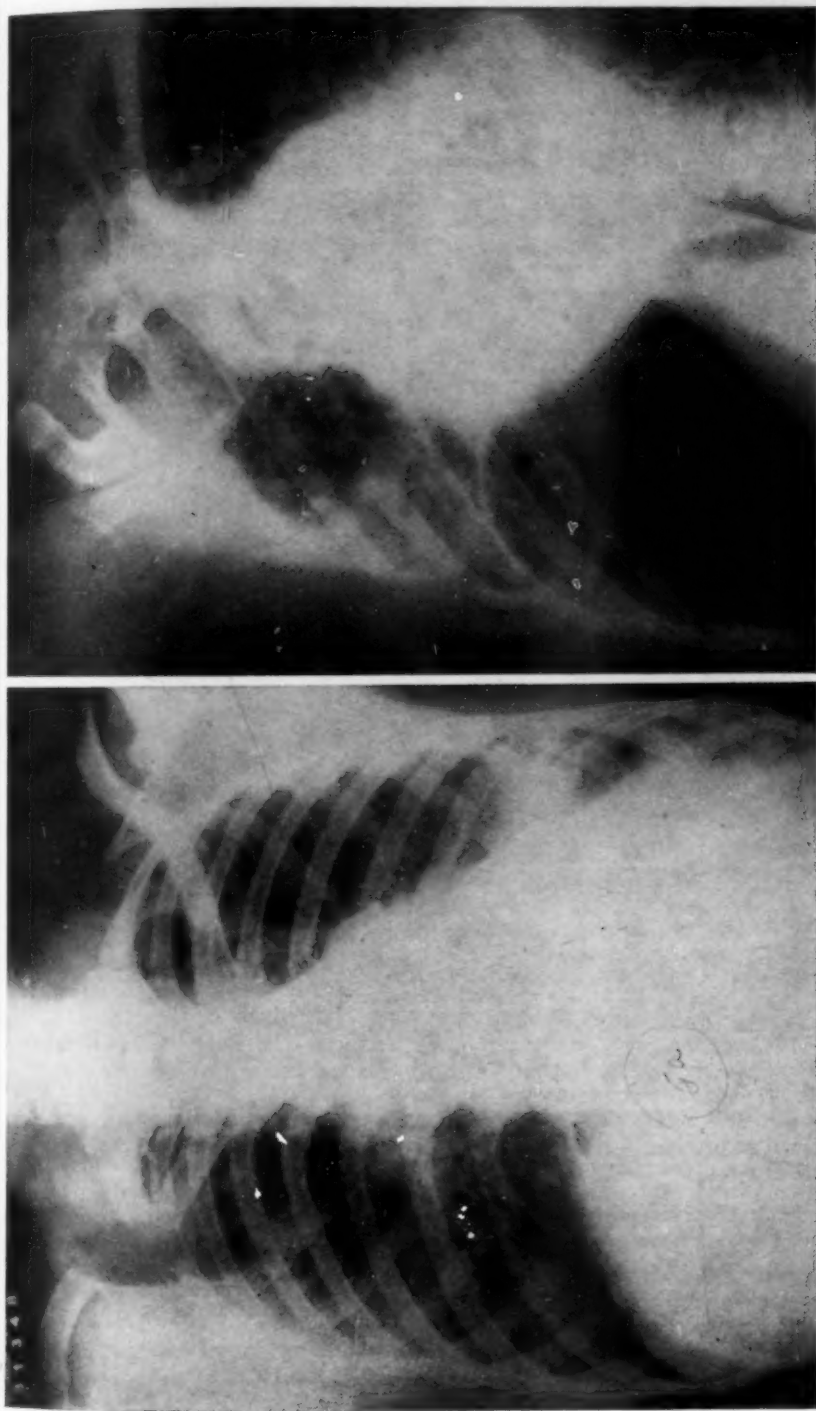


FIG. 9. A. X-ray of the chest in case 6 shows diffuse pulmonary infiltration and prominence of the pulmonary artery. B. Angiocardiogram in case 6, three seconds after injection of contrast medium, shows visualization of the pulmonary aneurysm.

101° F.; blood pressure 130 mm. Hg systolic and 62 mm. diastolic; diminished resonance and bronchovesicular breath sounds over the right hemithorax posteriorly, with moist râles and bronchophony over the same area; a rough systolic and a blowing diastolic murmur, both of moderate intensity, over the pulmonic area, resulting in a to-and-fro murmur (figure 1).

Laboratory findings: 9 gm. of hemoglobin; sedimentation rate of 64 mm. per hour; sputum positive for acid-fast bacilli; electrocardiogram within normal limits (figure 7). Roentgenologic examination revealed, in addition to the pulmonary parenchymal lesion, a prominent pulmonary artery with an increase in intensity of pulsation in this area; diodrast visualization (figure 9) showed the area of aneurysmal

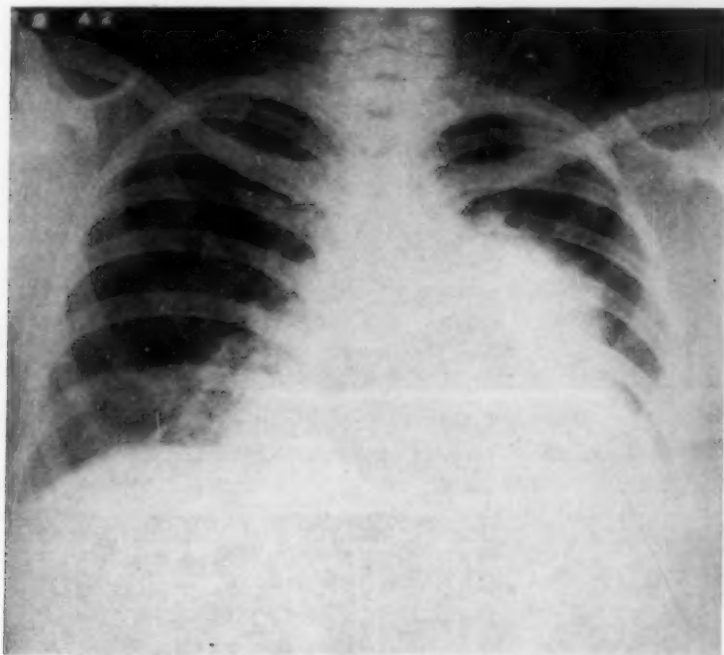


FIG. 10A. X-ray of the chest in case 7 reveals a marked prominence in the region of the pulmonary artery.

formation to be in the pulmonary artery. Cardiac catheterization studies were within normal limits (table 1). A diagnosis of mycotic aneurysm of the pulmonary artery was made.

The patient is being treated with pneumoperitoneum and the administration of streptomycin at present.

Case 8. A 43 year old colored female was admitted to Charity Hospital on October 15, 1941, complaining of dyspnea at rest for the previous 10 months. The only other complaint was nocturnal cough, productive of a small amount of phlegm. She had one child. There was no history of abortions.

Positive points on physical examination were sluggish reaction of the pupils to light; blood pressure 184 mm. Hg systolic and 96 mm. diastolic; heart enlarged slightly to right and left to percussion; a low-pitched systolic murmur of moderate intensity and a high-pitched, diminuendo diastolic murmur at the pulmonic area (figure 1).

Laboratory examination: Red blood cell count of 5.2 mil. per cu. mm.; white blood cell count of 8,900, with a normal differential; urinalysis: trace of albumin; phenol-sulfonphthalein test: 60 per cent excretion in the first hour; Kline and Kolmer tests strongly positive on repeated examinations. Electrocardiogram showed slurred QRS complexes, right axis deviation, and a low T in Lead I (figure 7). Fluoroscopy and roentgenograms of the chest revealed cardiac enlargement to the right and left,

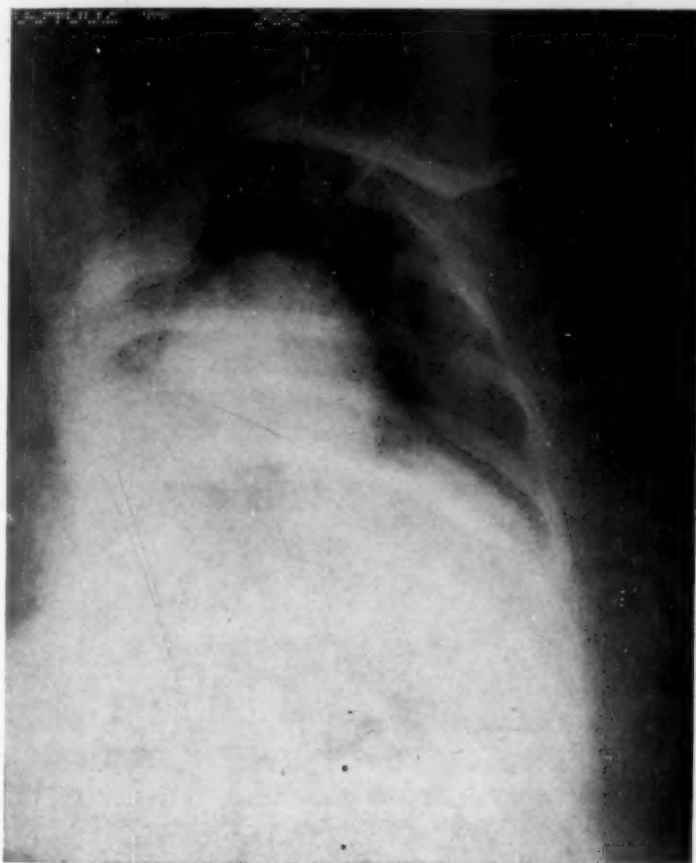


FIG. 10B. Angiocardiogram in case 7 two and one-half seconds after the injection of the contrast medium, shows the pulmonary artery aneurysm visualized.

with massive enlargement of the pulmonary artery; diodrast visualization of the cardiac chambers revealed the pulmonary artery aneurysm to be well visualized 2.5 seconds following injection; the serial roentgenograms showed the dye to be out of the pulmonary artery region in 8.5 seconds, and the aorta was well visualized and appeared normal (figure 10).^{*} A diagnosis of pulmonary artery aneurysm, probably on a syphilitic basis, was made.

^{*} These angiocardiograms were made by Dr. James Gouaux.

DISCUSSION

In six of our cases, the presence of murmurs in systole and diastole brought up the possibility of patent ductus arteriosus. The machinery murmur of a patent ductus arteriosus is continuous throughout systole and diastole in most cases. This is necessarily so if any difference in pressure

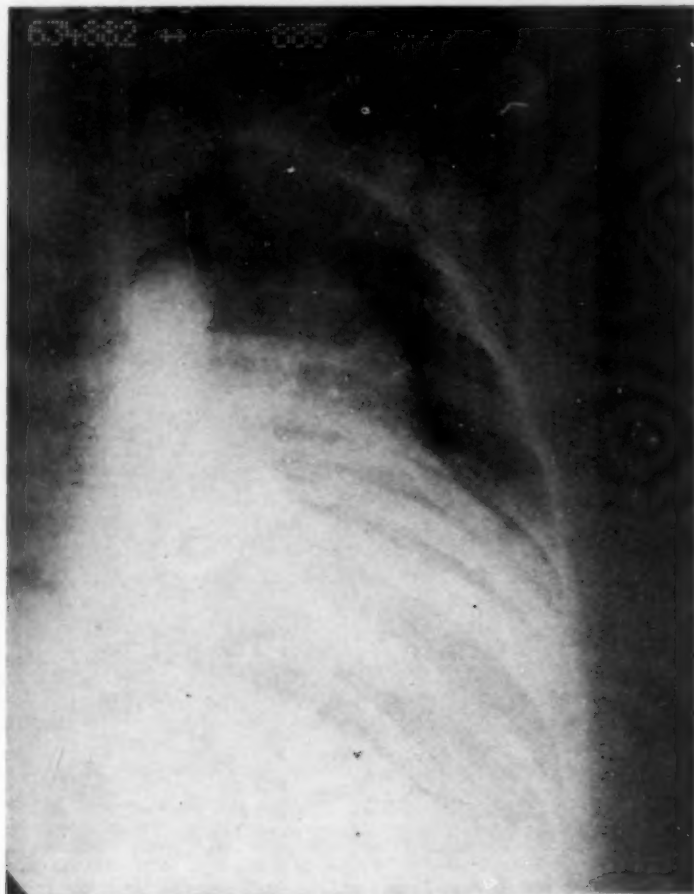


FIG. 10C. Angiocardiogram in case 7 four and one-half seconds after the injection of the contrast medium.

exists between the pulmonary artery and the aorta in systole and diastole. The murmur may tend to fade out in late diastole; however, it should continue past the second sound. On the other hand, a to-and-fro murmur, as found in our six cases, consists of a systolic crescendo murmur, usually a second sound, and a diastolic decrescendo murmur. There is frequently a

pause between the two phases. The continuous murmur associated with a patent ductus arteriosus tends to have the same quality throughout, with increased intensity in systole, whereas the to-and-fro murmurs tend usually to be low-pitched and rough in systole and high-pitched and blowing in



FIG. 10D. Angiocardiogram in case 7 seven and one-half seconds after the injection of the contrast medium, shows the aorta visualized. The pulmonary artery aneurysm is seen to be distinct from the aorta.

diastole. The differential characteristics of these two types of murmurs may be seen in figure 11. The systolic murmurs in cases 1, 2 and 3 are probably a result of pulmonary stenosis. The diastolic murmur in the first two is probably due to regurgitation through the pin-point valvular orifice which remained open in diastole. The murmurs in cases 4 and 5 are probably due to a valvular stenosis and insufficiency, although pulmonary incompetency

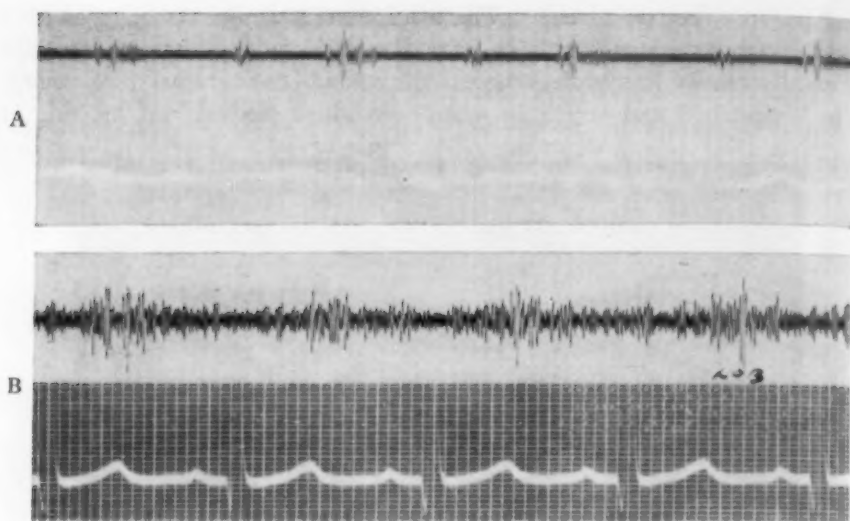


FIG. 11. A. Sound tracing shows early systolic and diastolic murmurs with an absence of any murmur in the last two-thirds of systole and diastole in case 4. B. Sound tracing shows a continuous murmur in a case of a patent ductus arteriosus.

and pulmonary artery dilatation may also play a part. In cases 6 and 7 the systolic murmur is probably produced by blood flowing into a dilated pulmonary artery; the diastolic murmur is believed to be due to a pulmonary incompetency.

Cases 4, 5, 6 and 7 demonstrate the application of venous catheterization to the evaluation of cardiac conditions other than congenital heart disease.

SUMMARY

1. Seven patients are reported with isolated pathologic lesions of the pulmonary valve or artery.
2. A diagnosis of congenital isolated pulmonary stenosis was made in three patients, and of acquired pulmonary stenosis and insufficiency in two cases, one due to rheumatic infection and one a result of bacterial endocarditis. Two patients have pulmonary artery aneurysms, one presumably on a syphilitic and the other on a mycotic basis.
3. It is pointed out that the to-and-fro type of murmur heard in six of the reported cases may be differentiated from the continuous murmur resulting from patent ductus arteriosus.

We wish to thank Mrs. Peggy Read and Miss Mary Alyce Jackson for their technical assistance.

BIBLIOGRAPHY

1. Greene, D. G., Baldwin, E. D., Baldwin, J. S., Himmelstein, A., Roh, C. E., and Courand, A.: Pure congenital pulmonary stenosis and idiopathic congenital dilatation of the pulmonary artery, *Am. J. Med.* **6**: 24-40, 1949.
2. Myers, G. B., Klein, H. A., and Stofer, B. E.: The electrocardiographic diagnosis of right ventricular hypertrophy, *Am. Heart J.* **35**: 1-40, 1948.
3. Pollack, H. A., Taylor, B. E., Odel, H. W., and Burchell, H. B.: Pulmonary stenosis without septal defect, *Proc. Staff Meet., Mayo Clin.* **23**: 516, 1948.
4. Clawson, B. J., and Bell, E. T.: Comparison of acute rheumatic and subacute bacterial endocarditis, *Arch. Int. Med.* **37**: 66-81, 1926.
5. Lehman, R. G.: Case report: acquired stenosis of pulmonary valve; death caused by *Staphylococcus aureus* septicemia and acute bacterial endocarditis, *Ohio State M. J.* **38**: 345-346, 1942.
6. Deterling, R. A., Jr., and Clagett, O. T.: Aneurysm of the pulmonary artery; review of the literature and report of a case, *Am. Heart J.* **34**: 471-499, 1947.

THE INITIAL ATTACK OF ACUTE MYOCARDIAL INFARCTION *

By THOMAS P. JACOBS, M.D., *New Rochelle, New York*

THIS study was undertaken in an attempt to clarify several of the clinical features of the initial episode of acute myocardial infarction, and to correlate these data with laboratory and necropsy findings in order to cull therefrom information useful in the diagnosis and early prognosis of the disease.

MATERIAL

The material consists of the records of 88 patients treated at the Roosevelt Hospital from 1934 to 1947. The cases have been rigidly selected from the records of over 800 cases with the diagnosis of acute myocardial infarction. Thirty-three of those presented were observed by the writer.

The criteria for selection of cases suitable for inclusion in this study are the following:

1. The diagnosis of acute myocardial infarction was established by unequivocal serial electrocardiographic evidence, or by postmortem examination.
2. All cases selected were free from coexisting or complicating diseases which might have contributed to the development secondarily of acute myocardial infarction; for example, cases of infarction occurring postoperatively, or as a result of shock from any cause such as trauma or hemorrhage, or occurring terminally in those with debilitating diseases, were excluded. Diabetes mellitus and syphilis were not considered bases for exclusion.
3. An adequate history from the patient was necessary in order to rule out especially cases with a history of previous illness which might be construed as a prior attack of myocardial infarction.
4. Cases with histories of more than one previous attack of congestive heart failure were arbitrarily excluded, because of the frequent autopsy evidence of old infarcts in this group, despite a negative history for acute infarction.
5. All necropsied cases revealed acute myocardial infarction, with no evidence of a previous myocardial infarct.
6. Patients dying shortly after admission to the hospital were of necessity excluded because of paucity of data.

MORTALITY, AGE AND SEX

Of the group of 88 cases, 17 failed to survive the initial illness, a rate of 19.3 per cent. The immediate mortality is defined here as the mortality in

* Received for publication January 13, 1949.
From the Roosevelt Hospital, New York City.

the period of six weeks from the onset of the illness. The earliest death occurred three hours after onset, and the latest on the thirty-fifth day. Four died in the first 24 hours; six from the second to fifth day; two on the tenth day, and one each on the thirteenth, fifteenth, nineteenth, twenty-eighth and thirty-fifth days.

The series included 82 males and only 6 females. The average age of the males was 54.0 years; that of the females, 59.7 years. Both figures are statistically not significant due to the small number of cases, but they are found to be quite comparable to those of Conner and Holt.¹ In their similar study of 287 cases, 84.7 per cent were males; 75 per cent of their patients suffered the initial attack before the sixty-first year, and one-third before the fifty-first year. We find similar age and sex ratios in our cases (table 1). Conner and Holt also found that in women the greater proportion of cases occurred later in life, with few women under the age of 51. Levine² gives a ratio of seven males to two females; Clawson³ found a ratio of 4.2:1 in

TABLE I
Age and Sex Incidence

Age	Females	Males	Total
36-40	1	3	4
41-45	0	11	11
46-50	0	15	15
51-55	0	19	19
56-60	2	18	20
61-65	2	7	9
66-70	0	4	4
71-75	0	5	5
76-80	1	0	1
Total Cases	6	82	88

1,215 autopsies of myocardial infarction. Bland and White⁴ found a ratio of 84 per cent males to 16 per cent females. Rathe⁵ gives 2.4:1 for the initial attack, with an average of 58 years for the men and 63.4 for the women. Master et al.⁶ found an average age of 54 years for the initial attack. They gave the peak incidence for the females in the 55 to 59 age group, and, for the males, in the 50 to 54 age group.

Coronary occlusion is peculiarly rare in the female under the age of 40. White⁷ mentions one female age 22. Glendy, Levine and White⁸ found a ratio of 96 men to four women in 100 cases of infarction under the age of 40. Levine and Rosenbaum⁹ found that 86 per cent of their females were 50 or over, while 65 per cent of their males were in the same age division; they had 20 patients from 30 to 39 years, and all were men.

This very real discrepancy in the sex incidence in the younger age groups remains unexplained. It is of some interest that the only female in our series under 55 was 40, and had submitted to a bilateral oöphorectomy at the age of 18.

Wide variations in mortality statistics for the initial attack of infarction are found in the literature. Master¹⁰ gives the lowest at 8 per cent; Conner and Holt¹ found it to be 16.2 per cent; Levine² found a 53 per cent mortality for all attacks; Woods and Barnes¹¹ found a 41.7 per cent mortality rate for men and 75 per cent for women, with a range of 28.1 per cent for those under 50, progressively through 84.6 per cent for those over 70. Bland and White⁴ found a four week mortality of 19 per cent in 200 cases, with a higher rate for females. They noted that patients dying early were, on the average, 10 years older than those surviving. Master, Dack and Jaffe⁶ found a 23.2 per cent mortality for initial attacks, with a sharp rise over the age of 60. In all of their cases of infarction the mortality rose from 15.4 per cent in the fourth decade to 42.0 per cent in the seventh; the women had a mortality rate of 32 per cent, as compared with 28 per cent for the men.

In our few cases there is a mortality rate for the men of 14 per cent in those 60 years and under, rising to 37 per cent for patients over 60. Two of the six females died aged 56 and 77. The overall rate of 19.3 per cent closely approximates that given by Bland and White,⁴ Master et al.⁶ and Conner and Holt.¹

RACIAL INCIDENCE

This series of 88 cases is composed of 87 whites and one Negro, a male. Of the whites, 21 were of thoroughly mixed stock: 27 were Jews, and 11 of these were Russian Jews; 16 of the remainder were Irish, seven Italian, five Greek, four French, and the others were scattered through the German, Austrian, Turkish and Czech nationalities. None was of Portuguese or Spanish stock, although considerable numbers of Puerto Ricans are seen at the hospital. The Scandinavians also were not represented, nor were the Chinese, although these latter are seen infrequently on the wards.

The percentage of Jews in the entire group (30.7) is high, but little higher than the ratio of Jews admitted for all reasons. Nevertheless, Glendy, Levine and White⁸ state that there is higher incidence among Jews, most pronounced in the younger age groups. Conclusive evidence on this point is lacking in the literature.

Johnston,¹² studying autopsy records, found a higher incidence of myocardial infarction among whites, particularly white males. Burch and Voorhies,¹³ working in a large hospital with a fairly even ratio of white to Negro admissions, established a corrected ratio of 7:2 (white to Negro) for coronary occlusion.

SEASONAL INCIDENCE

We find that the initial attack occurred almost equally in all months of the year. There was no predilection for the cooler six months: October through March: 43 cases. April through September: 45 cases.

Master et al.¹⁴ found a similar year-round incidence, but Bean¹⁵ and Bean and Mills¹⁶ found coronary occlusion much more frequent in the winter.

Although there are more attacks of and deaths from congestive heart failure during the colder months, particularly in the northern portion of the United States, a definitely higher seasonal incidence for the initial attack of myocardial infarction has not been demonstrated.

OCCUPATION

Study of the occupations of the people comprising this group of cases, drawn largely from the lower income brackets, suggests no particular hazardous type of work as a predisposing factor. Master, Dack and Jaffe¹⁴ reviewed the occupations of 522 patients with coronary occlusion and found no definite stratum of society affected. In a study of 100 cases of acute myocardial infarction, Chambers¹⁷ found no correlation with either environment or occupation. Rathe⁵ also found occupation of no significance. No convincing evidence has been presented by any writer that any occupation, including the practice of medicine, predisposes towards acute myocardial infarction or its forerunner, coronary arteriosclerosis.

WEIGHT AND BUILD TYPES

Only seven patients in this group could be classified as thin or poorly nourished, while 23 were definitely obese, some markedly so. Many fitted into the pyknic classification, having short wide chests, with a blunt angle formed by the ribs at the xiphoid, and well-developed shoulder girdle and arm musculature. The hyposthenic type of build was rare, and usually found in the older patients.

Levine² feels that body build and obesity are definite related factors in the development of this disease. In their excellent study of coronary disease in young compared to old age groups, Glendy, Levine and White⁸ found that 70 per cent of those under 40 were "robust," and that one-third of these were obese; whereas only 2 per cent of those over 80 were obese, while 83 per cent were lean and thin.

TOBACCO AND ALCOHOL

Twelve patients were nonsmokers, and about 50 per cent were "heavy" users of nicotine. One patient volunteered the information that during the week prior to the onset of the attack, transient substernal pain occurred each of several times that he smoked.

Data on the use of alcohol were considered unreliable and incomplete.

Master et al.¹⁴ found no relationship between the use of tobacco and coronary thrombosis. Glendy, Levine and White⁸ found 6.7 per cent nonsmokers in their younger group and 44.2 per cent nonsmokers in the older,

but smoking in younger people is much more prevalent today than 50 years ago. Blumer¹⁸ found no significant differences in the use of alcohol and tobacco in 150 patients with coronary disease compared to 150 controls, while White and Sharber¹⁹ obtained similar results in the study of 750 patients with angina pectoris. Bryant and Wood²⁰ discovered one case of pure tobacco angina in a 68 year old physician, and published electrocardiograms on this patient revealing marked RS-T deviations while smoking, without elevation of heart rate. Their studies indicate that minor T wave changes induced by smoking usually do not represent myocardial ischemia, however, but rather a physiologic response to an increase in heart rate, the usual effect of smoking. Even though nicotine may cause coronary spasm in the occasional patient, there is no evidence available that the resultant ischemia is sufficient to cause infarction per se; but, on theoretical grounds, sensitivity to nicotine could be a contributory factor in causing further ischemia in a heart with previously damaged blood supply.

Fitzhugh and Hamilton²¹ stated that the onset of the attack in five of their 100 cases of coronary occlusion followed directly on the heels of an episode of alcoholic excess. The elements of associated extreme overactivity, gorging and, finally, exhaustion, make any evaluation of the abuse of alcohol very hazardous. The use of alcohol in moderate amounts in selected cases of angina pectoris is frequently of value.²²

SYMPTOMS AND SIGNS

Angina Pectoris, Preliminary Pain, and Other Premonitory Symptoms: Thirty-five (39.8 per cent) of our cases formerly had experienced attacks of substernal, precordial or anterior chest pain during exertion or excitement. The duration of the syndrome angina pectoris was of less than one week prior to the infarction in eight patients; from one to four weeks in six; from five to 12 weeks in five, and over 12 weeks in 16.

In addition, we have noted the following types of warnings experienced in others prior to the actual attacks:

1. *Eleven* had attacks of anterior chest pain unrelated to exertion or excitement during the few days prior to the onset of unremitting pain.
2. As noted previously, *one* patient had a "smoking angina" during the week before the attack.
3. *Two* noticed increasing ankle edema for one week; in one man there was an associated postprandial epigastric pain for a few hours, seven days before the attack.
4. *Five* described the onset of breathlessness on exertion at some time during the preceding four weeks.
5. *Two* noted only a numbness and tingling of the arms in the few weeks before they became ill.
6. *Two* similarly developed a new cough.

7. *One* developed orthopnea only.
8. *One* suffered from breathlessness at rest.
9. *One* had the clearcut phenomena of sharp pain in the volar aspect of the left wrist accompanied by dyspnea for five minutes, two days before the attack.

In addition, others had symptoms of less clear relationship to the infarction. One man suffered a severe pain in the left arm briefly, just once, five months prior to the attack; two others experienced frequent "heartburn"; two had unexplained hemoptysis, with no other symptoms, and two more gave evidence of circulatory disease by developing intermittent claudication, 12 and six months prior to the attack.

There were only 29 of 88 patients who did not have warning that disease, usually circulatory disease, was present. In 39 of 59 who revealed previous symptoms, the symptoms were of recent development, within one month of the attack.

The overall figure of 39.8 per cent of our cases having prior angina (if the recently developed cases are included) is very close to those given by several authors.^{1, 8, 17}

Wearn,²³ reporting in 1923 on 19 fatal cases of myocardial infarction, found that six of them had angina coming on only weeks or months before the final event. Feil²⁴ stated that in one-half of the cases of coronary thrombosis the attack was preceded by pain unrelated to effort or emotion. (There were 11 such cases in this series.) Feil described this pain as usually mild, substernal or epigastric, more or less constant, burning or oppressive, and not relieved by rest or nitrites; its duration was from a few hours to a few weeks. Levine²⁵ stated that mild discomfort in the chest may precede the pain of infarction by a few days. Sampson and Eliaser²⁶ found, as a frequent preliminary symptom, an episode of prolonged precordial pain, occurring from one to 21 days before the attack; they also noted that in those with previous angina pectoris there was often a preceding attack of pain which was longer, more severe, and less easily relieved by nitrites.

Rathe⁵ found that, of 274 cases of initial infarction, 37 per cent had had previous angina of effort, 19.3 per cent had noted epigastric distress or pain not related to exertion, and 37 per cent had had a type of "preliminary pain" which was not severe but often burning, either retrosternal or epigastric. In addition, 32 per cent of his patients experienced unusual fatigue for two to six weeks before the attack.

HYPERTENSION

Fifty-eight of the series had neither a history of hypertension nor evidence of elevated blood pressure at any time during the hospital stay.

Of the remaining 30, or 34 per cent of the group, seven gave a history of hypertension but at no time had pressures exceeding 140 mm. Hg systolic

or 90 mm. diastolic; 12 had both a history of hypertension and elevated pressures under observation; and 11 had not known of their hypertension but revealed blood pressure elevation. Of this latter group, six had systolic and diastolic elevation, three systolic elevation only, and two diastolic elevation only. Since seven cases had a history of high blood pressure never confirmed by examination after the infarction, we are quite willing to concede the existence of another group which had previously undetected hypertension reduced to normal by the infarction. The literature in general supports a rather higher figure for preëxisting high blood pressure. Conner and Holt,¹ reporting initial attacks, found 33.9 per cent with preëxisting hypertension. Rathe,⁵ with first attacks, found 63 per cent. In a series including all attacks, Chambers¹⁷ found a 74 per cent incidence; Master et al.²⁷ found that 71 per cent of 207 non-fatal cases, and 49 per cent of 70 fatal cases, had hypertension. Levine² stated that more women have antecedent hypertension; Glendy et al.⁸ found that 16.6 per cent of their 100 cases under 40 had hypertension. Master et al.⁶ found that 25 per cent of the females under 35 and 90 per cent of those over 45, and that 80 per cent of the women and 56.5 per cent of the men, had high blood pressure. They found that hypertension did not affect the immediate prognosis, as have most other writers.

ACTIVITY AT ONSET OF ATTACK

The activity of the patient at the time the first symptom ushered in the attack of myocardial infarction was noted accurately in 69 cases. The activity preceding the onset of any preliminary symptoms was usually not ascertainable with accuracy. Of the 69, we find 14 sleeping, 15 walking, eight resting, six sitting at work, six standing, four "resting after a heavy meal," three lifting, three resting after heavy exercise, two carrying heavy loads, and one each riding in vehicles, walking upstairs, playing cards and urinating. Superficial analysis indicates that only 11 of 69 were engaging in or had just ceased participation in activities which included exercise or emotional excitement.

In 1937, Master, Dack and Jaffe,¹⁴ investigating 530 cases of myocardial infarction, found no relation of the onset to exertion or excitement. Again in 1939 the same group²⁸ reported on 973 attacks, and found 22.3 per cent sleeping, 30.7 per cent resting, and no definite relationship to exertion. In 1939 the same group²⁹ reported similarly on 1,440 attacks in 1,077 patients, with compensation cases excluded. They also investigated the relation of exertion to premonitory symptoms; the latter were present in 80 of 170 cases, and likewise did not seem to be related to exertion.

Fitzhugh and Hamilton,²¹ on the other hand, reported a very close relationship of unaccustomed, prolonged or violent exertion, fatiguing travel, emotional strain, gorging, intercourse and other activities to the onset of the attack. Paterson³⁰ felt that the activity of the patient hours or days prior

to the onset of the symptoms is usually important, via the mechanism of elevated blood pressure, increased capillary pressure, and rupture of capillaries in the intima of coronary vessels, leading directly to thrombosis of the coronary artery at the site of intimal hemorrhage.

Boas³¹ found 25 cases related to unusual exertion, and in general supported Paterson's thesis.

FIRST SYMPTOM OF ATTACK

The first symptom noted by the patient was pain in 76 cases (86.4 per cent). For the remainder, the onset was ushered in by breathlessness in three, impending syncope in three, and a substernal oppressive sensation definitely not painful in two; one each had fever, thirst, gaseous eructation and syncope as the initial symptom.

In most cases where pain was the first symptom, when there had been preliminary pains or angina previously, there was either an increase in severity, a change in radiation, or an increase in duration to indicate that a change in the illness had occurred.

Of the 17 fatal cases, 14 were ushered in by pain, two by dyspnea, and one by impending syncope.

PAIN

Eighty-six patients experienced pain; only two did not.

1. *Character of Onset:* The pain came on suddenly in 77, fairly rapidly in five, and insidiously in six.

2. *Primary Site:* The primary site of the pain was located as substernal, precordial, or diffusely throughout the anterior chest in 77; epigastric in four; both epigastric and under the lower sternum in three; lower abdominal in one, and in the left forearm in one. The latter patient later had his arm pain referred to the precordium, where it gradually increased in intensity.

3. *Description of Pain:* One-fourth of the patients described their pain merely as "bad" or "severe," and three more as "moderate." In addition, 75 other adjectives were used in describing the pain of the remaining 61 cases. Some patients felt that the pain held two qualities at once, often combining a deep oppressive sensation with a more superficial sharp or sticking substernal pain of greater intensity. The adjectives "oppressive," "squeezing," "heavy," "like a vice," "grinding," "chocking," "dead feeling," "constricting," and "tight feeling growing to pain" were used 58 times. Less often the pain was noted as "burning," "catching," "pushing-out," "tearing," "cramplike needles" and "excruciating." The pain was merely "sharp" in eight cases. An analysis of the fatal cases shows no predilection for a type of combinations of pain useful in prognosis, but it is of mild interest that three of 17 fatal cases had abdominal pain and one had no pain.

4. *Duration of Pain until Admission:* Sixty-eight (77 per cent) of the group entered the hospital less than 24 hours after the onset of the attack; 43 of these were admitted within four hours of onset. Only four patients were admitted after the seventh day. Most entering after the first day were, in the interim, receiving medical care in their homes. Intense pain, collapse and apprehension sent the majority quickly to the hospital. Some of those who did not seek medical aid promptly were noted to have remittent or intermittent pain, with completely free intervals, and cyclic variations in the intensity of the pain. No patient admitted early or late had had unremitting severe pain for as long as one day, although a substernal soreness or heaviness was frequently present during relatively free intervals.³²

5. *Radiation:* The radiation of the pain was noted in all cases. In 19 (21.6 per cent) the pain remained localized. In the remainder there were 34 different combinations of radiation sites. The left arm and forearm were involved in 45 cases, the right arm in 22, the upper back in 12, the left shoulder in six, the lower jaw and teeth in four, and the neck in three. In 19 the left arm was the only site of radiation, while the right arm was the only site in but one case, where there was a sharp pain in the right wrist only, with the substernal pain. In eight there was spread to both arms and forearms, and in four more simply a numbness of both arms; in three there was radiation to the left shoulder alone, and in two to both shoulders and left arm.

In only two cases was the pain radiated to the interscapular area without concomitant spread to other sites; in dissecting aneurysm of the aorta, uncomplicated interscapular radiation is common.

All other combinations occurred but once each.

Analysis reveals that the left shoulder, arm or forearm were involved in two-thirds of all cases; that radiation to the upper back occurred often, but usually in combination with other radiations; and that although the right shoulder and arm were sites one-third of the time, it was rare for the pain to radiate there exclusively. Similarly, pain spread to the neck, throat, jaw, teeth or ears only twice, without other radiation.

We can conclude that it is exceptional for pain to radiate to any *one* site except the left upper extremity.

White⁷ found that pain occurred in 54 of 56 unselected autopsied cases of acute myocardial infarction; he emphasized the frequent absence of pain but presence of an oppressive sensation in its stead, and that older people often confuse dyspnea with pain. Levine² stated that pain may be absent, and that all degrees of pain may be present. Herrick³³ noted a few painless cases, and stressed the frequent simulation of an abdominal catastrophe. Wearn²³ found that the steady intense pain frequently changed to a dull ache in the same area, with a later return to former intensity apt to occur. Steincrohn³² described continuous pain with rhythmic regular or irregular variations in intensity. Rathe,⁵ studying 274 first attacks, found severe pain in 56 per cent and moderate pain in 13 per cent. Chambers¹⁷ found (as did

we) no correlation between the intensity or type of pain and immediate prognosis, but of his 21 per cent painless cases, half died, and of his eight cases with epigastric pain, five died. He found that when pain occurred in the epigastrium or right upper quadrant, it did not radiate. He found the left arm most frequently involved.

We have observed that infarctions in the older age group, those complicating surgical procedure and trauma, and those in Negroes are frequently painless, with sudden dyspnea as the chief symptom.

The higher incidence of painless infarctions noted in the literature is not applicable to the group studied here, which were initial attacks; it is possible that the initial infarction of a previously unscarred portion of the myocardium is more likely to result in the usual pain mechanism than infarction of an area already damaged.

GASTROINTESTINAL SYMPTOMS

Abdominal pain was excluded as a gastrointestinal symptom. No cases of nausea or vomiting occurring after an opiate had been given on admission were included. A few undoubtedly were given morphine before admission without our knowledge.

Vomiting occurred in 21 cases (24 per cent). Vomiting occurred in 35 per cent of the fatal cases, and in 21 per cent of the cases that survived. Three other nonfatal cases had nausea without vomiting. Eructation of gas occurred in two fatal and two other cases, while diarrhea was present in four fatal and two other cases.

We find that gastrointestinal symptoms are frequent, occurring in about one-third of all cases, and that they certainly are not of favorable prognostic significance. White⁷ agreed that vomiting was common but was more often induced by opiates. Herrick³³ emphasized the frequency of gastrointestinal symptoms.

DYSPNEA

Shortness of breath or rapid or labored breathing was given as a symptom or noted as a sign in 41 of 88 cases; it was present in 10 of 17 fatal cases. In some it represented an inability to catch the breath while pain was present, while in others it was the most prominent symptom, often indicating frank heart failure. Orthopnea was noted in comparatively few patients, occurring in seven fatal and 15 nonfatal cases. Wearn²⁸ observed the frequency of dyspnea with the relative infrequency of orthopnea.

All degrees of breathlessness were seen, but in the majority it was only mild to moderate distress. Many writers feel that, next to pain, dyspnea is the most common symptom, but it should be emphasized that 53 per cent of our cases never experienced altered breathing at any time during the illness.

Dyspnea is naturally more common in fatal cases, since many die in congestive heart failure.

WEAKNESS

Weakness of variable degree, in some verging on prostration, and in a few causing complete collapse, was a very common subjective and objective finding:

	Mild Weakness	Marked Weakness	Total
Fatal Cases (17)	1	14	15
Nonfatal Cases (71)	5	45	50
Total (88)	6	59	65

Some degree of weakness was present in 74 per cent of all cases. A marked degree of weakness was present in 63 per cent of the nonfatal and 82 per cent of the fatal groups. The not infrequent presence of weakness, in the absence of other signs of shock, gives it more diagnostic significance; its more usual presence with shock makes it less helpful. So many nonfatal cases exhibit extreme weakness as to make it of no value as a prognostic sign.

The complete absence of weakness is somewhat more useful, in that fatal cases seldom fail to show some degree of collapse.

DIAPHORESIS

Sweating is mentioned briefly by most writers as one of the symptoms of acute myocardial infarction seen during the shock phase.⁷ It was a common symptom and sign, and we found it in 58 per cent of the nonfatal and in 47 per cent of the fatal cases. It was rarely present in the absence of some degree of shock, and was usually profuse and associated with a cool skin. The symptom (or sign) is not useful prognostically.

SYNCOPE

We found fainting, usually of brief duration, present in 11 cases (12.5 per cent). In these 11 cases it was the initial symptom in no case, but it occurred during the first hours of the attack in all.

The most striking observation in connection with loss of consciousness is that it occurred in nine cases of posterior wall infarction and in only two of anterior wall infarction. Only one case was fatal.

The frequent observation of bradycardia, of arrhythmias, and of involvement of the posterior portion of the interventricular septum in cases of posterior wall infarction would lead one to predict such a discrepancy. We are not able to agree with Roth³⁴ who, in his discussion of the differential diagnosis between massive pulmonary embolism and acute posterior wall myocardial infarction, stated that syncope practically never occurs in the cardiac lesion.

It also appears that syncope is in itself not a poor prognostic sign, probably because it is due not to shock but to temporarily reduced cardiac output.

Four other cases gave a history of a sensation of impending syncope of brief duration.

APPREHENSION

A sense of impending death or milder degrees of apprehension were subjective or objective findings in 35 patients (40 per cent). In most cases the degree of pain appeared to govern the amount of fright. There was no higher percentage of fearful patients among those that died.

PALPITATION

Awareness of rapid, forceful or irregular heart action was not submitted as an early symptom by any patient in this series. A few noted palpitation later in the course, particularly when premature contractions were present.

COUGH

Cough was present in 16 per cent of the cases, and was usually associated with pulmonary congestion or edema.

FEVER

No patient complained of chills, and fever was offered as a complaint on admission in but two cases.

Eighty-three cases were suitable for study in regard to fever; four were eliminated because they died so early in their course, and the day of onset of the attack was in considerable doubt in another.

1. Of the 70 nonfatal cases, the highest rectal temperature recorded occurred on the average 2.9 days after the onset of symptoms; of the 13 fatal cases, the peak temperature occurred on an average of 4.5 days after onset.

2. The nonfatal group had maximum temperatures ranging from 98.8° F. to 103.8° F., with an average high of 101.39° F. The fatal cases had maxima between 100.4° F. and 104.4° F., with an average of 102.20° F.

3. No fatal case living for more than one day was afebrile. Only two nonfatal cases failed to reveal a rectal temperature of 100.0° F. or more at some time in the course.

The distribution of the maximum temperatures is recorded in table 2.

The admission temperature of the 62 cases entering the hospital sometime during the first day of the attack averaged 98.7° F. for 54 nonfatal and 99.1° F. for eight fatal cases.

The temperature usually remained normal for the first day.

Five cases of the 62 entering on the first day had admission temperatures of 100.0° F. or over. Two of these were among the eight fatal cases in the group of 62, while three were among the 54 cases that survived.

Sixteen of 20 patients entering on the second or higher day of attack had a temperature of 101° F. or more on admission. The presence of fever at any time after the first day is to be expected.

White⁷ stated that the prognosis is poor if the fever ranges over 103° F. Rathe felt that a fever of 101° F. or over for five days or longer was of no particular prognostic significance. In general we agree with this, as many of our nonfatal cases showed this type of curve. Chambers¹⁷ found an average admission rectal temperature of 101.7° F. for his fatal cases, whereas ours were only 99.1° F., but the day of onset of symptoms was not included in his calculations.

The complete absence of fever during the early days of an illness with other symptomatology of acute myocardial infarction should make the at-

TABLE II
Maximum Temperatures

Rectal Temperature (Fahrenheit)	Nonfatal	Fatal	Total
Under 101	8	2	10
101.0 to 101.8	25	2	27
102.0 to 102.8	26	5	31
103.0 to 103.8	11	2	13
104.0 and over	0	2	2
Total Cases	70	17	83

tending physician extremely wary. Only rectal temperatures will suffice, because, due to frequent accompanying reduced peripheral blood flow, oral and axillary temperatures are notoriously unreliable.

HEART RATE

1. *Admission Heart Rate* (table 3): Rates under 80 per minute were commonplace, present here in 52 per cent of all cases. Marked tachycardia was relatively infrequent and, when present, often represented auricular flutter or fibrillation. Of the 17 fatal cases, eight had admission heart rates of over 100, while only nine of 71 nonfatal cases revealed tachycardia. On the other hand, bradycardia did not appear to be associated with poor prognosis. It will be noted that there is a wide spread of figures for admission pulse rate, so that the admission heart rate is of little diagnostic help except when a bradycardia is present.

2. *Maximum Heart Rate* (table 4): We find that 50 per cent of the total group never had rates over 100. In general it will be seen that a rate over 120 was not favorable.

TABLE III
Admission Heart Rate

Beats/Min.	Fatal	Nonfatal	Total
Under 40	0	3	3
41- 60	1	10	11
61- 80	2	30	32
81-100	6	19	25
101-120	7	7	14
121-140	0	2	2
141 and over	1	0	1
Total Cases	17	71	88

The day of illness on which the most rapid rate occurred was ascertained in 67 nonfatal cases. In 70 per cent this was found to be the first, second or third day, with equal distribution. In an additional 23 per cent the fastest rate occurred during the next four days, while in the remainder a high rate was seen after the first week, usually in conjunction with signs of further myocardial infarction or of pulmonary infarction.

Rathe⁵ found that a rate of over 100 during the first week was an ominous sign, and observed it in 76 per cent of his early fatal group (dead in one month), while only 25 per cent of the remainder of his cases showed it. Chambers¹⁷ found the average admission rate higher in his fatal cases, as do we.

Persistent tachycardia, whether of the sinus variety or due to an arrhythmia, is more often seen in those patients who do not survive the initial illness.

BLOOD PRESSURE

1. *Admission Systolic Pressure* (table 5): There was observed a wide range of systolic levels in both fatal and nonfatal groups. Readings of over 140 are less common in the fatal cases.

A considerable error of selection enters into these figures, as some of the most severely shocked patients, dying within minutes after admission, are

TABLE IV
Maximum Heart Rate*

Beats/Min.	Fatal	Nonfatal	Total
61- 80	0	8	8
81-100	1	33	34
101-120	6	25	31
121-140	4	5	9
141 and over	1	0	1
Total Cases	12	71	83

* Five cases dying within a few hours of admission are not included.

not included in this study for lack of data. Many others are never seen by any medical attendant. Nevertheless, it will be seen that an admission level of less than 80 is not necessarily fatal: only one of six in this group did not survive.

2. *Systolic Pressures After One Week:* After a week of bed rest it was found that, in the nonfatal group, over 25 per cent had levels under 100, while only three cases exhibited hypertensive figures (over 140), even though many of these had known previous hypertension or elevated admission pressures.

3. *Systolic Pressure at Discharge:* At the completion of a four to 12 week hospital stay with clinical recovery, 20 per cent had systolic levels of 91 to 100, and 10 per cent were over 140, while the remaining 70 per cent were normotensive. No patient had a level of over 170, and only one was slightly under 90. The duration of this pressure lowering effect among

TABLE V
Admission Systolic Blood Pressure Levels

Mm. of Hg	Fatal	Nonfatal	Total
Under 71	0	3	3
71- 80	1	2	3
81- 90	2	4	6
91-100	1	8	9
101-110	2	11	13
111-120	3	12	15
121-130	4	6	10
131-140	3	8	11
141-150	0	5	5
151-170	0	5	5
171 and over	1	7	8
Total Cases	17	71	88

former hypertensives was studied by Master et al.,²⁷ who found that one-third of hypertensive patients "permanently" lost their high blood pressure.

4. *Pulse Pressure* (table 6): Admission pulse pressure readings are compiled in table 6. We feel that their value is limited because of the variable number of hours from onset of symptoms to actual admission.

A wide variation in pulse pressures is evident. Although a pulse pressure of 30 or less is seen in a higher percentage of fatal cases, the difference is not striking. Master et al.²⁷ found a high mortality with a pulse pressure of less than 20; Rathe⁵ observed a figure of 20 or less in 20 per cent of his early fatal group, while only 0.7 per cent of his late fatal cases and none of his survivors had such low pulse pressures. We have here seven survivors with an admission pulse pressure of 20 or less.

Some observers^{17, 27} describe two types of blood pressure fall with this disease: either a sharp early drop, or a gradual descent over a one to three

week period. Master et al.²⁷ found that some showed no fall for a week or more after the onset; we had no such cases, all dropping during the first week if at all. Chambers¹⁷ noted as a good prognostic sign an early return of the blood pressure to normal. Our data are not clear on this point; a number of fatal cases showed rises from low admission levels, with subsequent secondary falls as the general condition deteriorated.

White⁷ stated that the pressure may be high early because of the pain, and he has seen cases where the blood pressure was normal before and after the infarct but high at the time of the attack. He also found the pressure unaffected in many smaller infarcts. Master et al.²⁷ also described the early transitory rise. We have seen it in a few patients not in this study, always in hypertensives, reaching levels far over their usual pressures for a few hours during the pain.

TABLE VI
Admission Pulse Pressure

Mm. of Hg	Fatal	Nonfatal	Total
10 or less	0	0	0
11-20	2	7	9
21-30	6	9	15
31-40	4	19	23
41-50	3	16	19
51-60	1	11	12
61 and over	1	9	10
Total Cases	17	71	88

The most important finding in regard to blood pressure, we feel, is that it is very often entirely normal on admission, even in some of the most widespread infarctions; a sharp early descent or a gradual late descent is helpful diagnostically to only a moderate degree, for many noncardiac illnesses cause a similar reduction in blood pressure, particularly with prolonged bed rest.

QUALITY OF THE HEART SOUNDS ON ADMISSION

1. The heart sounds were described as distant, weak, muffled, of poor quality, or "tic-tac" in 65 cases. 2. The tones were "imperceptible" in three cases, of which one was fatal. 3. Good quality tones were present in two of 17 fatal cases (12 per cent), and in 18 of 71 nonfatal cases (25 per cent). 4. The first heart sound at the apex was frequently muffled or weak. 5. A split first sound was noted in two fatal cases. 6. A systolic murmur was present in 11 patients.

The poor quality of the heart sounds frequently encountered is of considerable diagnostic significance but of no prognostic importance. On the other hand, good clear forceful tones are more often heard in cases that survive.

CARDIAC ENLARGEMENT

Definite enlargement of the heart was present in 30 cases (34 per cent). Thirteen of the 30 had known either previous hypertension or elevated pressure at some time during observation. Eleven of the 30 were fatal cases. The probability of lesser degrees of enlargement not recognized by clinical or radiologic examination in a number of surviving cases is not denied.

Master, Dack and Jaffe⁶ found enlarged hearts in 59.8 per cent of cases of myocardial infarction in a study not limited to first attacks. There was progressive rise in incidence of from 35.9 per cent, in those under 40, to 78.3 per cent in patients over 70. More women (74 per cent) than men (58 per cent) had enlarged hearts. This would parallel the higher incidence of hypertension in women who suffer cardiac infarction.

ARRHYTHMIAS

(a) Premature contractions were observed in 11 cases; seven of these had posterior wall infarctions, two were fatal. (b) Complete heart block was present in seven cases; it was often associated with other arrhythmias (auricular flutter and fibrillation), and with the Stokes-Adams syndrome. Only three had it on admission; one of the seven died; generalized convulsions occurred in one case with intermittent attacks of complete block, alternating with wild bursts of irregular rapid heart action. Four cases were associated with anterior and three with posterior wall infarction. (c) Auricular fibrillation was present in three cases, one had it on admission. The others were of the paroxysmal type, coming on late in the course. One associated with anterior wall infarction died; the two with posterior infarction survived. (d) Auricular flutter was proved in four cases; in one it alternated with fibrillation, and there was complete block with another; three of the four died. Two had anterior, and two posterior wall infarction. (e) There were no examples of paroxysmal tachycardia. (f) Sinus bradycardia was present in 11 cases on admission, with heart rates of less than 60. Ten of the 11 were nonfatal. Seven were associated with posterior, three with anterior and one with lateral wall infarction.

In this small series, neither sinus bradycardia nor complete heart block appears to be of poor prognostic significance. Levine² stated, however, that complete block is associated with a poor outlook. He also found premature contractions in 35 of 145 cases and auricular fibrillation in 34 of the same group; these arrhythmias were not of significant prognostic import in his series. Four of his five cases with paroxysmal ventricular tachycardia died.

Chambers¹⁷ found that occasional premature contractions were meaningless but that, if they persisted, the gravity of the prognosis was greatly increased. Similarly, he found persistent sinus tachycardia associated with

a high early mortality. Ten of his 100 cases had auricular fibrillation, and seven died; all three of his cases of auricular flutter lived.

Askey and Neurath,³⁵ in a study of 1,247 cases of myocardial infarction, found a 7.7 per cent incidence of auricular fibrillation. The immediate mortality for the whole series was 51.5 per cent; for those with transient fibrillation, 58.6 per cent, and for those with persistent fibrillation, 89.4 per cent. They concluded, reasonably, that auricular fibrillation of over 24 hours' duration greatly increased the gravity of the prognosis.

GALLOP RHYTHM

Gallop rhythm was present in 17 cases (20 per cent); three were fatal; 15 were associated with anterior wall infarction, and include the three fatal cases. Only eight of 17 revealed gallop on admission, and one of these died.

Shillito et al.³⁶ found gallop present in 28 per cent of 50 closely observed uncomplicated cases of myocardial infarction; they noted that its persistence is associated with a poorer prognosis.

Rathe⁵ observed gallop in 51 per cent of his fatal cases, and in 8 per cent of his surviving group. Levine² found gallop very common with a rapid rate, disappearing as the heart slowed. Thompson and Levine³⁷ observed that gallop occurring early in the course was an extremely unfavorable sign, and that the presence of gallop in those cases without hypertension was more unfavorable.

PERICARDIAL FRICTION RUB

A transient pericardial friction rub of from six to 72 hours' duration was detected in 17 cases, an incidence of 20 per cent. Six of the fatal cases had the sign, while an additional four fatal cases died within the first day of illness before they logically had opportunity to develop fibrinous pericarditis, so that six of 13 fatal cases living over one day developed the sign.

Friction rub was first heard on the third day of illness nine times, on the second day twice, and once each on the fourth, fifth and seventh days. In the remaining three cases the rub was heard later in the course, coincident with other findings indicative of further myocardial infarction.

Fourteen of the cases in which a friction rub was present had anterior wall infarction, two had posterior wall, and one posterolateral infarction.

The rub was loudest most often in the third or fourth interspace to the left of the sternum, but occasionally was present only at the apex, as in the case with posterolateral infarction.

The incidence of this sign is given variously in the literature from 9 per cent to 20 per cent.^{2, 17, 5, 30, 38} Levine² found it better heard more often near the nipple than near the sternum. Chambers¹⁷ reported a 10 per cent incidence with an associated high mortality.

Friction rub is a very helpful diagnostic sign; its absence is of no diagnostic significance, while its presence definitely worsens the prognosis.

COMPLICATIONS

1. *Congestive Heart Failure*: Heart failure was the most frequent complication, being present in 15 fatal and 17 nonfatal cases, an overall ratio of 35 per cent. Pulmonary congestion and edema were the most common findings; dependent edema was infrequent, while enlarged tender livers were quite rare, and were present in no case on admission.

2. *Additional Myocardial Infarction*: Fifteen cases (17 per cent) had definite evidence of a further myocardial infarction, all occurring between the second and seventh weeks of illness. Six of these died, and autopsy confirmed the clinical impression in each case.

3. *Pulmonary Infarction*: Pulmonary infarction occurred in six cases with reasonable certainty, and in a probable two more, an incidence of 9 per cent; all survived. None of the autopsied cases revealed evidence of either pulmonary embolism or infarction. None of this series of cases received anticoagulant therapy.

4. *Angina Decubitus*: Angina decubitus developed in four patients; one had attacks of substernal pain radiating to the left arm associated with profuse diaphoresis confined to the left half of the body exclusive of the head and neck, while another had pain induced by emotional upheavals also associated with marked sweating. Another four cases developed angina of effort upon mobilization and previous to discharge.

5. *Other complications* included hypostatic pneumonia (four cases); urinary tract infection (two cases), and one case each of cerebral vascular accident, thrombophlebitis, cardiac rupture, cardiac aneurysm, convulsions, prolonged severe weakness, hematemesis of undiscovered origin, arteriosclerotic gangrene of the foot, and severe mental depression with neurodermatitis.

Chambers¹⁷ noted a 33 per cent incidence of heart failure, and 65 per cent of his fatal cases were in failure as opposed to 25 per cent of those that survived. Master et al.⁶ found that 33 per cent of their deaths were due primarily to heart failure, while another 16.5 per cent were ascribed to failure plus shock.

Woods and Barnes¹¹ found 10 per cent of their deaths due to pulmonary embolism. This is the usual estimate given. Chambers¹⁷ observed pulmonary embolism in 5 per cent of his 100 cases, and all lived, findings very similar to ours.

In our experience, the chief causes of death after the first 48 hours are congestive heart failure and further myocardial infarction, while in the earlier period, shock, "forward failure" and probably cardiac standstill and ventricular fibrillation account for the deaths, except for a few, usually hypertensives, who die rapidly of acute pulmonary edema.

ASSOCIATED DISEASES

1. *Diabetes Mellitus*: Diabetes was present in five patients (6 per cent), two of whom died. In a large series Master et al.⁶ found an incidence of

11.2 per cent, with a frequency of 4.8 per cent for those under 50 years of age and an incidence of 17 per cent for those 60 or over. This was not a study of initial attacks. They noted a mortality among the diabetics of 39.3 per cent, as opposed to a death rate of 27.5 per cent for the remainder. They remark that only one female in 10 failed to reveal either diabetes or hypertension.

2. *Syphilis*: Latent syphilis was present in four cases; two more had syphilitic aortitis; all lived.

LABORATORY DATA

1. *Electrocardiographic Location of Infarct*: Both more frequent incidence of and higher mortality for infarction of the anterior wall of the left ventricle may be seen in table 7. Of the five cases dying before electrocardiograms were performed, two were anterior wall, two posterior wall, and the other a combined anterior-posterior infarction.

TABLE VII
Electrocardiographic Location of Infarct

	Fatal (12)	Nonfatal (71)	Total
Anterior	10	32	42
Posterior	2	33	35
Anterolateral	0	4	4
Mixed	0	2	2
Total Cases	12	71	83

Baer and Frankel,³⁹ in a study of 321 cases, found a higher incidence and mortality for anterior wall infarction, and reported that 71 per cent of their autopsied cases revealed this type of lesion. Rathe⁵ found that most of his early fatal cases were due to anterior wall infarction. Shillito et al.³⁰ and Chambers,¹⁷ along with most other investigators, reported similarly on a higher incidence for anterior infarction.

2. *Leukocytosis*: (a) At the time of admission, a white blood count of less than 10,000 white blood cells per cu. mm. was present in only 10 per cent of 86 cases. (b) An admission level of 12,000 to 25,000 was noted in 73 per cent. (c) There was no relatively higher mortality among 13 cases with admission levels of over 20,000. The only case having an admission count of 30,000 or above died. (d) Of the 71 cases having a white blood cell count performed subsequent to admission, only one failed to reveal a leukocytosis (over 10,000). (e) Three cases had a white blood cell count of over 25,000 after the day of admission; all died. (f) The highest white blood cell count was discovered during the first three days of illness in 69 per cent of the cases. (g) Exacerbation of leukocytosis after the seventh day invariably coincided with other evidences of fresh myocardial infarction, pulmonary infarction, or infection of the respiratory tract, leg veins, or

urinary system. (h) The highest white blood cell count was usually seen on an average of about one day before the peak temperature rise. (i) Polymorphonuclear neutrophilic response of over 80 per cent was seen in 50 per cent of the admission counts and in 64 per cent of the highest levels attained; there was a normal "poly" ratio in a surprisingly large number of sharply elevated counts; only 9 per cent of all counts had a neutrophilic response of over 90 per cent. There was no correlation between the degree of polymorphonuclear neutrophilic leukocytosis and mortality.

3. *Erythrocyte Sedimentation Rate*: The Cutler method of determining the sedimentation rate was utilized in all cases.

Of 64 cases having an erythrocyte sedimentation rate determination at some time during the first three hospital days, 45 (70 per cent) had rates of over 10 mm. per hour, and 27 (42 per cent) rates of over 15 mm. per hour. There was no correlation between mortality and early or marked elevation of the sedimentation rate. A large enough group had normal values on admission to make the test comparatively worthless in early diagnosis.

However, subsequent determinations revealed an elevation (over 10 mm. per hour) in 66 of 70 nonfatal cases, the rate reaching 16 mm. per hour or more in 60 of the 70. Only four cases revealed completely normal levels of 3 to 10 mm.

The peak elevation was found most often from the fourth to the eleventh day (70 per cent of nonfatal cases). The sedimentation rate continued elevated in a few cases when all other clinical and laboratory evidence of active pathology had ceased, but in the majority the rate had returned to normal by the sixth week or before.

Late elevation of the sedimentation rate is a useful finding in the diagnosis of acute myocardial infarction.

NECROPSY FINDINGS

Postmortem examinations were performed on 15 of 17 fatal cases.

In 10, recent coronary thrombosis was present in at least one of the major coronary vessels; in three more, arteriosclerotic complete occlusion of one or more vessels was present; the remaining two revealed gross evidence of severe arteriosclerotic process involving all coronary vessels, with marked narrowing but no complete occlusion in the larger branches.

1. Eight of the cases had been diagnosed anterior wall infarction by electrocardiogram. Six of these revealed occlusion of the anterior descending branch, and one occlusion of the anterior descending and circumflex branches. The eighth revealed considerable narrowing, but incomplete occlusion of all major branches. Infarction of the anterior wall was present in all eight. In addition, six showed evidence of infarction of the anterior portion of the interventricular septum; one also had infarction of the lateral

portion of the left ventricle, and another revealed a concomitant small posterior wall infarction. Four of these eight had mural thrombi in the left ventricle, one additional had a thrombus only in the right auricle. One case had no mural thrombi, but had a renal infarct. No other embolic phenomena were found in this group.

2. Two cases diagnosed posterior wall infarction by electrocardiogram were autopsied. In one the right coronary artery was thrombosed, with infarction of the posterior wall. The other revealed thrombosis of both the right coronary artery and the anterior descending branch of the left coronary artery, with resultant infarction of the posterior wall, interventricular septum, and the posterolateral portion of the wall of the left ventricle. No mural thrombi or embolic phenomena were present in either case.

3. Five cases came to necropsy before electrocardiograms were taken. Three revealed occlusion of the anterior descending branch, two of these by thrombosis. One of them had infarction of the anterior wall and septum, another of the base of the anterior wall only, and the third revealed the septum and anterior and posterior walls all infarcted. The fourth case showed severe arteriosclerosis of all major branches without complete occlusion, and infarction of the posterior wall only. The last case revealed arteriosclerotic occlusion of both the anterior descending and circumflex branches, with infarction of the posterior wall and interventricular septum. Of the above five, one had mural thrombi in the left ventricle, another in the left auricle. No embolic lesions were found. One of the anterior wall infarctions was complicated by a ruptured left ventricle with hemo-pericardium.

The heart was markedly hypertrophied in six of 15 examinations, and moderately hypertrophied in two more. Two hearts showed old focal myocardial fibrosis; in none was there evidence of previous infarction. No hearts revealed infarction of the wall of the right ventricle. Infarction of one or more papillary muscles of the mitral valve was a common finding.

The electrocardiogram correctly localized the major area of infarction in all 10 cases.

SUMMARY OF VARIOUS FACTORS IN EFFECT ON IMMEDIATE MORTALITY

1. *Factors affecting prognosis unfavorably:*

- (a) Age over 60.
- (b) Abdominal pain.
- (c) Vomiting.
- (d) Diarrhea.
- (e) Prolonged high fever (over 103° F.).
- (f) Prolonged severe weakness.
- (g) Tachycardia.

- (h) Persistent auricular flutter or auricular fibrillation (over 24 hours).
- (i) Gallop rhythm.
- (j) Pericardial friction rub.
- (k) Congestive heart failure.
- (l) Blood pressure less than 80 systolic.
- (m) Cardiac enlargement.
- (n) Anterior wall infarction.
- (o) Leukocytosis over 25,000.

2. *Factors exerting no appreciable effect on prognosis:*

- (a) Sex.
- (b) Race.
- (c) Occupation.
- (d) Season.
- (e) Previous hypertension.
- (f) Previous angina.
- (g) Intensity, character, duration or radiation of chest pain.
- (h) Dyspnea.
- (i) Fever up to 103° F.
- (j) Diaphoresis.
- (k) Syncope.
- (l) Apprehension.
- (m) Leukocytosis up to 25,000.
- (n) Marked elevation of sedimentation rate.

3. *Factors of good prognostic significance:*

- (a) Age under 50.
- (b) Low grade fever.
- (c) Lack of weakness.
- (d) Normal heart rate or bradycardia.
- (e) No or little lowering of blood pressure.
- (f) Admission systolic pressure of over 140 mm. Hg.
- (g) Normal size of heart.
- (h) Freedom from arrhythmias.
- (i) Strong clear heart sounds.
- (j) Lack of heart failure, gallop rhythm, friction rub.
- (k) Posterior wall infarction.

DISCUSSION

The pathogenesis of atherosclerosis is still quite obscure, but the evidence of a metabolic defect associated with hypercholesterolemia in many patients with coronary artery disease is incontrovertible.⁴⁰ On the other hand, we

know that merely a high intake of fat and cholesterol does not directly lead to hypercholesterolemia and probably not to cholesterol deposition in normal individuals⁴¹; nevertheless, there is a strong suspicion that a reasonably high exogenous cholesterol intake, as well as one or more basic intrinsic defects, is necessary for the deposition of cholesterol-containing atheromatous plaques. It is probable that the high incidence of coronary arteriosclerosis in obese young adults is intimately connected with the cholesterol and fat metabolism problems. Of more interest is the strikingly higher incidence of coronary disease in young adult males compared to females; this may well be due to either an inhibiting action of estrogens or an accelerating action of androgens on the atherosclerotic process. The relationship of cholesterol to the complex steroid chemicals composing the various sex hormones provides an obvious open line of investigation. Studies of both male and female castrates might be useful.

No explanation of the considerably lower incidence of coronary disease in the Negro is available; differences in diet and social conditions do not appear to be of consequence.

The greater incidence of coronary occlusion and myocardial infarction in the hypertensive segment of the population may be related to two factors: the hypertrophied myocardium may have previously outstripped its blood supply to some extent, rendering it more vulnerable to coronary closure, or the higher pressures may predispose to capillary rupture with subsequent thrombosis.⁴²

The status of exertion as an immediate precipitating factor in the pathogenesis of coronary thrombosis remains clouded, for the causative exertion may have occurred hours or days prior to the symptoms of infarction; evaluation of a history of stress or exertion prior to the onset of preliminary symptoms, when present, is subject to gross error, for the memory of the patient for more remote events will be obscured by the more recent dramatic catastrophe.

It has been made abundantly clear that coronary occlusion is not always followed by myocardial infarction. Blumgart et al.⁴³ have demonstrated that the hearts of patients with angina pectoris usually have one or two of the three major coronary trunks occluded, and that increasing severity and frequency of attacks of angina may denote thrombotic or arteriosclerotic occlusion of a previously patent vessel. Their studies show conclusively that infarction frequently occurs when the vessel most recently occluded is the one which has been supplying collateral circulation to an area of endangered myocardium, that is, an area which had previously been threatened by the reduction or complete cessation of blood flow from its primary source by occlusion, severe narrowing or thrombosis.

Any factor initiating increased heart rate or work will cause lesser or greater degree of myocardial ischemia in hearts where the coronary arteries are narrowed, with one or more main trunks usually occluded. If the

ischemia is of brief duration, the resulting myocardial changes will consist of tiny areas of necrosis, which are later followed by fibrosis; or, in lesser degrees of ischemia, the anoxemic changes may be completely reversible to normal. It is at this time that we may get the preliminary symptoms, such as pain, increased breathlessness, heartburn, belching and epigastric distress.⁴⁴ Those cases in which prolonged chest pain is not followed by the usual manifestations of infarction we term coronary insufficiency or coronary failure.⁴⁵ The two chief factors which determine whether the myocardial damage will be slight to reversible, or, on the other hand, infarction of a sizable area of muscle, are the extent of the available collateral circulation and the amount of work the heart is called on to perform during the crucial hours and days following the episode of preliminary symptoms. It is at this point that the physician can be of aid, chiefly by firmly ordering the patient to bed for from one to three weeks, and, secondarily, by administering vasodilating medications in a judicious manner. These measures may in many instances prevent the infarct, or limit its extent.

SUMMARY

1. The clinical picture and laboratory data of 88 cases of the initial attack of acute myocardial infarction have been presented, and in 15 cases correlated with necropsy material.
2. An effort has been made to emphasize those features of diagnostic importance, and to evaluate those findings which may aid in more accurate immediate prognosis.
3. Factors in the pathogenesis of coronary artery disease and myocardial infarction which are of apparent fundamental importance have been discussed.
4. A plea is made for extremely conservative handling of patients with possible impending myocardial infarction, in the belief that the latter catastrophe may sometimes be averted by comparatively simple measures.

BIBLIOGRAPHY

1. Conner, L. A., and Holt, E.: The subsequent course and prognosis in coronary thrombosis, *Am. Heart J.* **5**: 705-719, 1930.
2. Levine, S. A.: Coronary thrombosis; its various clinical features, *Medicine* **8**: 245-415, 1929.
3. Clawson, B. J.: Incidence of types of heart disease among 30,265 autopsies with special reference to age and sex, *Am. Heart J.* **22**: 607-624, 1941.
4. Bland, E. F., and White, P. D.: Coronary thrombosis with myocardial infarction ten years later, *J. A. M. A.* **117**: 1171-1173, 1941.
5. Rathe, H. W.: Myocardial infarction; clinical features and prognosis, *J. A. M. A.* **120**: 99-103, 1942.
6. Master, A. M., Dack, S., and Jaffe, H. L.: Age, sex, and hypertension in myocardial infarction due to coronary occlusion, *Arch. Int. Med.* **64**: 767-786, 1939.
7. White, P. D.: *Heart disease*, 3d Ed., 1947, The Macmillan Company, New York.

8. Glendy, R. E., Levine, S. A., and White, P. D.: Coronary disease in youth: comparison of 100 patients under 40 with 300 persons past 80, *J. A. M. A.* **109**: 1775-1781, 1937.
9. Levine, S. A., and Rosenbaum, F. F.: Prognostic value of various clinical and electrocardiographic features of acute myocardial infarction. II. Ultimate prognosis, *Arch. Int. Med.* **68**: 1215-1231, 1941.
10. Master, A. M.: Incidence of acute coronary artery occlusion, *Am. Heart J.* **33**: 135-145, 1947.
11. Woods, R. M., and Barnes, A. R.: Factors influencing immediate mortality rate following acute coronary occlusion, *Proc. Staff Meet., Mayo Clin.* **16**: 341-345, 1941.
12. Johnston, C.: Racial differences in the incidence of coronary sclerosis, *Am. Heart J.* **12**: 162-167, 1936.
13. Burch, G. E., and Voorhies, N. W.: Study of incidence of coronary occlusion and angina pectoris in white and Negro races, *Am. J. M. Sc.* **198**: 685-690, 1939.
14. Master, A. M., Dack, S., and Jaffe, H. L.: Factors and events associated with onset of coronary artery thrombosis, *J. A. M. A.* **109**: 546-549, 1937.
15. Bean, W. B.: Infarction of the heart; clinical course and morphologic findings, *Ann. Int. Med.* **12**: 71-94, 1938.
16. Bean, W. B., and Mills, C. A.: Coronary occlusion, heart failure, and environmental temperatures, *Am. Heart J.* **16**: 701-713, 1938.
17. Chambers, W. N.: Acute myocardial infarction, a study of 100 consecutive cases, *New England J. Med.* **235**: 348-352, 1946.
18. Blumer, G.: The relation of the use of alcohol and tobacco to coronary occlusion, *J. A. M. A.* **102**: 1177 (correspondence), 1934.
19. White, P. D., and Sharber, T.: Tobacco, alcohol and angina pectoris, *J. A. M. A.* **102**: 655-657, 1934.
20. Bryant, J. M., and Wood, J. E., Jr.: Tobacco angina, *Am. Heart J.* **34**: 20-34, 1947.
21. Fitzhugh, G., and Hamilton, B. E.: Coronary occlusion and fatal angina pectoris, *J. A. M. A.* **100**: 475-480, 1935.
22. Falk, O. P. J.: Treatment of coronary artery disease, *J. A. M. A.* **134**: 491-496, 1947.
23. Wearn, J. T.: Thrombosis of the coronary arteries, with infarction of the heart, *Am. J. M. Sc.* **165**: 250-276, 1923.
24. Feil, H.: Preliminary pain in coronary thrombosis, *Am. J. M. Sc.* **193**: 42-48, 1937.
25. Levine, S. A.: Clinical heart disease, 3d Ed., 1945, W. B. Saunders Company, Philadelphia.
26. Sampson, J. J., and Eliaser, M., Jr.: Diagnosis of impending acute coronary artery occlusion, *Am. Heart J.* **13**: 675-685, 1937.
27. Master, A. M., Jaffe, H. L., Dack, S., and Silver, N.: Course of blood pressure before, during, and after coronary occlusion, *Am. Heart J.* **26**: 92-107, 1943.
28. Master, A. M., Dack, S., and Jaffe, H. L.: Precipitating factors of coronary occlusion; further observations on the mode of onset of a large series of cases with particular emphasis on the role of effort and excitement, *Indust. Med.* **8**: 327-331, 1939.
29. Master, A. M., Dack, S., and Jaffe, H. L.: Activities associated with the onset of acute coronary occlusion, *Am. Heart J.* **18**: 434-443, 1939.
30. Paterson, J. C.: Relation of physical exertion and emotion to precipitation of coronary thrombosis, *J. A. M. A.* **112**: 895-897, 1939.
31. Boas, E. P.: Angina pectoris and cardiac infarction from trauma or unusual effort, with consideration of certain medicolegal aspects, *J. A. M. A.* **112**: 1887-1892, 1939.
32. Steincrohn, P. J.: New observation helpful in the diagnosis of coronary thrombosis, *Ann. Int. Med.* **14**: 495-501, 1940.
33. Herrick, J. B.: Clinical features of sudden obstruction of the coronary arteries, *J. A. M. A.* **59**: 2015-2020, 1912.
34. Roth, I. R.: Differential diagnostic problems in acute pulmonary embolization, *Am. J. Med.* **4**: 493-502, 1948.

35. Askey, J. M., and Neurath, O.: Prognostic significance of auricular fibrillation in association with myocardial infarction, *Am. Heart J.* **29**: 575-580, 1945.
36. Shillito, F. H., Chamberlain, F. L., and Levy, R. L.: Cardiac infarction; the incidence and correlation of various signs, with remarks on prognosis, *J. A. M. A.* **118**: 779-781, 1942.
37. Thompson, W. P., and Levine, S. A.: Diastolic gallop rhythm; note on certain factors influencing prognosis, *Am. Heart J.* **9**: 129-134, 1936.
38. Baer, S., and Frankel, H.: Studies in acute myocardial infarction. I. Clinical picture and diagnosis, *Ann. Int. Med.* **20**: 108-114, 1944.
39. Baer, S., and Frankel, H.: Studies in acute myocardial infarction. III. Diagnosis and location of infarct by electrocardiogram, *Arch. Int. Med.* **73**: 286-289, 1944.
40. Morrison, L. M., Hall, L., and Chaney, A. L.: Cholesterol metabolism, blood serum cholesterol and ester levels in 200 cases of acute coronary thrombosis, *Am. J. M. Sc.* **218**: 32-38, 1948.
41. Steiner, A.: Significance of cholesterol in coronary arteriosclerosis, *New York State J. Med.* **48**: 1814-1818, 1948.
42. Paterson, J. C.: Capillary rupture with internal hemorrhage as a causative factor in coronary thrombosis, *Arch. Path.* **25**: 474-487, 1933.
43. Blumgart, H. L., Schlesinger, M. J., and Davis, D.: Studies on the relation of clinical manifestations of angina pectoris, coronary thrombosis, and myocardial infarction, to the pathologic findings, *Am. Heart J.* **19**: 1-91, 1940.
44. Winter, R. E.: A prodromal syndrome of coronary occlusion, *New York State J. Med.* **48**: 1940-1942, 1948.
45. Freedburg, A. S., Blumgart, H. L., Zoll, P. M., and Schlesinger, M. J.: Coronary failure, *J. A. M. A.* **138**: 107-114, 1948.

ATYPICAL PNEUMONIA TREATED WITH STREPTOMYCIN: A PRELIMINARY REPORT ON THE EFFECTIVENESS OF STREPTOMYCIN IN ATYPICAL PNEUMONIA *

By FRANCIS P. KING, M.D., *Atlanta, Georgia*

ATYPICAL pneumonia, until recently, has been considered a disease for which there was no specific treatment. With the announcement of two new drugs that apparently are specific cures for this disorder, aureomycin^{1,2} and chloromycetin,³ another infectious disease was added to the already long list of those amenable to specific therapy.

In reporting the use of aureomycin in atypical pneumonia, Finland, Collins and Wells⁴ presented two cases of atypical pneumonia that appeared to respond dramatically to streptomycin. They also pointed out that they were able to find reported only two other cases of atypical pneumonia treated with streptomycin, and in these no benefit was noted. Recently Pulaski and White⁵ reported one more case in which streptomycin failed to influence the course of the disease. However, they did not give their criteria for diagnosis, only that "atypical pneumonia developed following bronchitis."

Following the report of Finland, Collins and Wells,⁴ an investigation was begun in an Army station hospital on the effectiveness of streptomycin in primary atypical pneumonia of unknown etiology. Ten cases of atypical pneumonia were treated, all showing marked immediate improvement. In some cases the improvement may have been coincidental with natural recovery. However, an attempt was made to select the most severe cases observed for this series. For this reason the cases were chosen carefully, and treatment with streptomycin was begun only after an interval of at least several days following hospitalization. In most cases a trial of penicillin therapy was given for two or more days before using streptomycin.

The criteria for diagnosis were definite pneumonia (by physical signs and chest roentgenograms) that was slow in onset without characteristic chill, rusty sputum and pleuritic pain. In each instance sputum culture was obtained and, in most, blood culture was taken before antibiotics were given. In no case was a pathogenic organism cultured. In each case cold agglutinins were tested and, in all but one, significant titers developed. Atypical pneumonia can at best be diagnosed early in its course only by exclusion, and this makes it difficult to evaluate early treatment. Perhaps, instead of using the name "atypical pneumonia," the term "non-bacterial pneumonia" would be preferable.

* Received for publication January 16, 1950.

From the Medical Service, Grady Memorial Hospital.

Each patient had a similar clinical course, characterized by a remittent fever associated with mild chills followed by profuse sweats. The fever could be promptly reduced by aspirin (10 gr.), which was administered frequently. In spite of the fact that some of the patients developed a temperature of over 104° F., none was seriously ill and all had only mild symptoms of headache, weakness and feverishness. Dizziness (lightheadedness) was a prominent symptom. If the disease was encountered early in its course, often no signs of pneumonia were discernible by careful physical examination in spite of obvious pulmonary infiltration by roentgen-ray. Later in each case, showers of medium moist râles could be heard over the involved area, and these usually persisted following clearing of the consolidation on the roentgen-ray film.

Each case was treated with 2 gm. daily of streptomycin for five days in divided doses every six hours. The dosage was chosen arbitrarily and no attempt was made to determine the minimum dosage required. No toxic effects of streptomycin were observed. Penicillin was usually given in dosage of 50,000 units every three hours, although this varied from case to case. Aspirin and codeine were given as needed for discomfort, and a liquid preparation of ammonium chloride was given for cough.

Reported here in detail are five cases of atypical pneumonia treated with streptomycin. Five other cases were treated also during this time; but because these cases were less severe, the improvement, although prompt, was not as striking as the ones presented here. In each case treated there were prompt subsidence of the fever and improvement in symptoms. It is significant to point out that no case failed to improve immediately. The most striking objective evidence was the temperature course. Usually the patient became afebrile within 24 hours. The chest findings cleared more slowly, and no marked difference was noted between the untreated cases and those treated with streptomycin. This may be attributable to the fact that, because of delay in administering streptomycin, pneumonia was developed fully before specific treatment was begun. The patients became symptomless in two to three days in spite of the fact that showers of râles could be heard over a large area of the chest.

CASE REPORTS

Case 1. An 18 year old white soldier was admitted to the hospital on April 29, 1949. He had been well until the day before admission, when he developed stuffiness, rhinorrhea, dizziness and nonproductive cough associated with substernal soreness. The past history was otherwise noncontributory.

Physical examination revealed slight injection of the pharynx. In the right lower anterior chest there were increased tactile fremitus, dullness to percussion, pectoriloquy and many fine moist inspiratory râles. The examination was otherwise normal.

The leukocyte count on admission was 7,850, with 75 per cent neutrophils and 25 per cent lymphocytes; the hemoglobin was 13.9 gm. Urinalysis and Kahn test

were negative. Sputum culture on April 29 and May 3 grew *Streptococcus viridans* and *Neisseria catarrhalis* as the predominating organisms, respectively. A blood culture on May 3 was negative. Blood counts on May 2 and May 5 were also normal.

A roentgenogram of the chest on April 29 showed pneumonic infiltration just above the right diaphragm adjacent to the heart. On May 4 x-ray showed further extension of the pneumonia obliterating the right diaphragmatic shadow and extending to the fourth anterior interspace.

In spite of his remittent fever, which each day reached above 103° F., he had symptoms only of dizziness, cough, slight headache, weakness and feverishness. Penicillin, 50,000 units every three hours, was started on May 1, and was continued for two days without evidence of response. Streptomycin, 0.5 gm. every six hours, was started on May 3 and continued for five days. There was a prompt subsidence of the fever so that within 24 hours he was afebrile, and symptoms improved with a sensation of feeling stronger and with disappearance of the headache and dizziness. His chest findings cleared slowly, however, and many râles could still be heard on

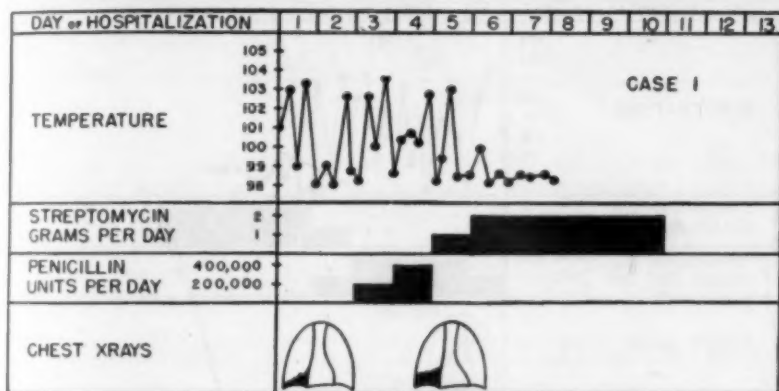


FIG. 1.

May 9, in spite of the fact that he felt well and was anxious to be discharged. He was allowed to resume full activity gradually and was discharged on May 12. Cold agglutinin titer on May 5 was less than 1:4, and on May 10 was 1:64.

Case 2. A 21 year old white soldier was admitted to the hospital on April 27, 1949. Two and a half days before he had developed headache, followed the next day by chills, fever, sweating, malaise, lassitude and cough productive of brownish sputum. These symptoms continued until admission.

On physical examination the tonsils were enlarged and the pharynx was injected. In the left lower posterolateral lung field many fine moist inspiratory râles were heard and breath sounds were suppressed, but no dullness was noted. There were no other abnormal findings.

Urinalysis and Kahn test on admission were negative; the leukocyte count was 14,000, with 75 per cent neutrophils and 25 per cent lymphocytes; the hemoglobin, 13.5 gm. Blood count on May 2 showed 12,700 leukocytes, with 80 per cent neutrophils, 18 per cent lymphocytes, and 2 per cent eosinophils. Sputum culture on admission showed *Neisseria catarrhalis*, and on May 2 *Streptococcus viridans* as the predominating organism. A blood culture on April 27 was negative.

Roentgenogram of the chest on April 29 showed pneumonic infiltration of the left lung field. A second film on May 3 showed further extension of the pneumonia.

The patient was given penicillin, 50,000 units every three hours, and symptomatic therapy. In spite of the persistent remittent fever up to 104° F., he had few complaints other than cough, weakness and slight headache, and he never appeared seriously ill. Penicillin appeared to have no effect and was discontinued on May 1; streptomycin, 0.5 gm. every six hours, was started on the same day and continued for five days. The next day his temperature did not exceed 99.6° F., and he was afebrile thereafter. His symptoms of cough and headache also disappeared and his strength returned, but his chest findings cleared slowly. He was allowed full activity gradually and was discharged on May 9. The cold agglutinin titer on May 2 was 1:64.

Case 3. A 24 year old white infantry soldier was admitted to the hospital March 11, 1949. He had been well until March 9, when he developed malaise and lassitude, followed the next morning by sore throat and nonproductive cough which persisted until admission. The past history was noncontributory.

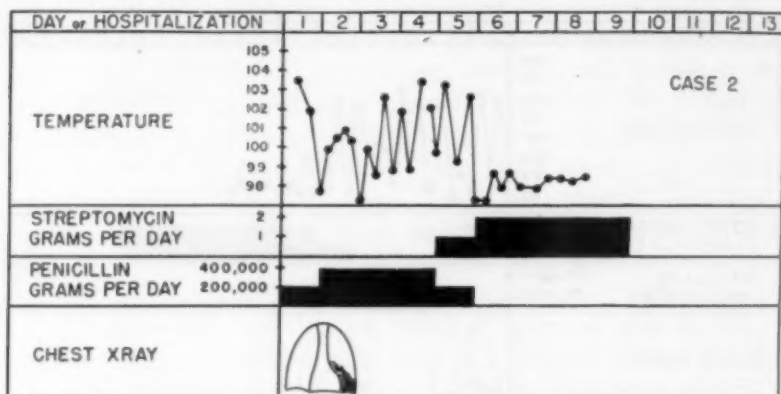


FIG. 2.

On physical examination there was injection of the pharynx without exudate. The lungs appeared to be clear and no abnormalities were noted on the remainder of the examination. The temperature was 102° F.

Urinalysis, Kahn test and stool examination were negative. The leukocyte count was 10,000, with 70 per cent neutrophils, 29 per cent lymphocytes, and 1 per cent eosinophils; hemoglobin was 13.5 gm.

Roentgenogram taken on admission showed a sharply demarcated infiltration in the lateral superior portion of the right lower lung, increased markings spreading out from the right hilar region, and infiltration radiating from the left hilar region.

For the next four days there was a daily elevation of temperature from normal in the morning to 102° F. in the afternoon, which was associated with dizziness, headache, weakness and lassitude. The cough continued and was at times very severe, but it was still nonproductive and no sputum could be obtained. On the second day after admission, occasional wheezes were heard over the right upper posterior lung field. During the next several days these were replaced by medium and fine moist inspiratory râles. Penicillin, 50,000 units every three hours, was begun on the day after admission. In spite of the intensive penicillin therapy the patient remained ill, with continued chilly sensations, fever, headache and dry cough.

On March 16, five days after admission, streptomycin was begun, 0.5 gm. every six hours, and the dosage of penicillin was changed to 50,000 units every six hours. There was a prompt subsidence of fever and of dizziness and headache, and some immediate diminution in the cough and chest findings, with gradual clearing during the next six days. No sputum culture was obtained because the cough continued to

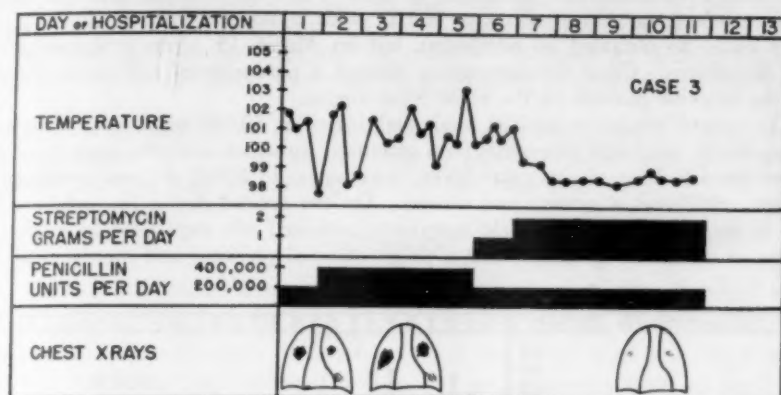


FIG. 3.

be nonproductive. The sedimentation rate remained elevated for some time, although the patient felt well. He was gradually allowed to resume activities about the ward and was discharged to duty March 26, 1949. Cold agglutinin titer on March 21 was 1:256.

Case 4. A 19 year old white soldier was admitted to the hospital March 13, 1949. Several days before admission he had noticed a sore throat, which had subsided.

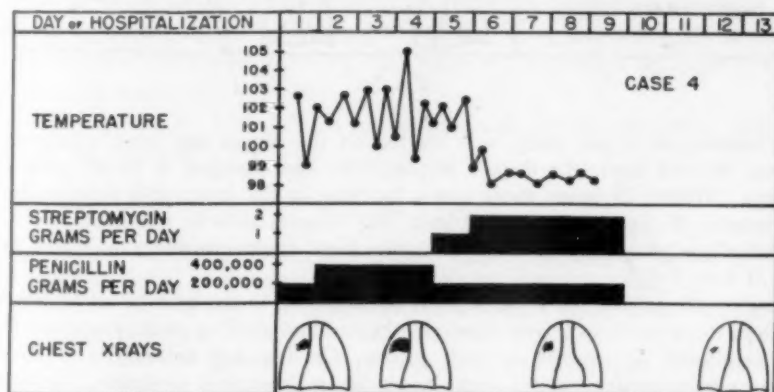


FIG. 4.

Four days before, he had noted malaise, lassitude, frontal headache, and a cough productive of a slight amount of green sputum. On the next day he felt aching pain in his extremities. On admission he complained of severe pain beneath his fingernails. There was no past history of rheumatic fever. The temperature was 103° F. The tonsils were injected and enlarged, and some of the crypts were filled with

exudate; the posterior cervical lymph nodes were slightly enlarged. The chest was entirely clear. There were no abnormalities detected in the joints or fingernails, and the remainder of the examination was normal.

Urinalysis and Kahn test were negative. The leukocyte count was 12,950, with 63 per cent neutrophils and 37 per cent lymphocytes; the hemoglobin was 15.1 gm. and the corrected sedimentation rate was 26 mm. An electrocardiogram was normal. Leukocyte count on March 21 was 10,100, with a normal differential count. No sputum could be obtained on admission, but on March 15, alpha streptococci were found on culture. Chest roentgenogram showed a parenchymal infiltration radiating from the anterior portion of the right hilar region.

The patient was given aspirin, fluids and penicillin, 50,000 units every three hours. The headache, joint and fingernail pain gradually subsided over the next three days. He continued to have an irregular fever, ranging up to 103.6° F., and complained of weakness, chilliness, dizziness and sweats. On the second day a few wheezes were heard in the right upper lung field anteriorly, followed two days later by moist râles. Because of continued symptoms and a progression of physical and roentgen-ray find-

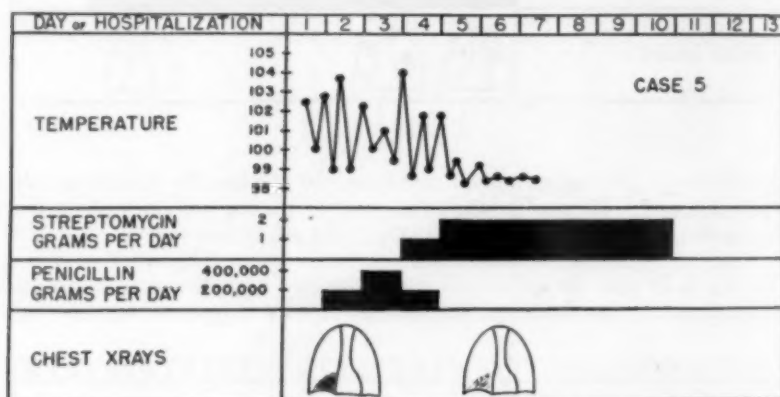


FIG. 5.

ings, streptomycin, 2 gm. daily, was started on the fourth day after admission and continued for five days; the dosage of penicillin was changed to 50,000 units every six hours. Within 24 hours there was a decrease in the fever, and disappearance of the symptoms of dizziness and weakness. He became afebrile within 36 hours, and was gradually allowed to resume full activity. Cold agglutinin titers on March 21 and March 31 were 1:128.

Case 5. A 24 year old white soldier was admitted to the hospital on May 9, 1949. On each of the three days before admission he had had shaking chills, fever and sweating, not relieved by aspirin or fruit juices. On the day before, he developed a moderate nonproductive cough, slight headache, malaise and weakness. Because he had had malaria in the South Pacific in 1944 and a recurrence in 1947, he thought he had malaria. On examination the pharynx was diffusely injected without exudate. The right thorax lagged on inspiration, and over the right posterior lower lung field there were dullness, increased tactile fremitus and whispered voice sounds, and bronchial breathing. No other abnormalities were noted.

Urinalysis and Kahn test were negative. The leukocyte count was 11,850, with 72 per cent neutrophils, 27 per cent lymphocytes, and 1 per cent eosinophils. Throat

and sputum culture on May 9 showed *Streptococcus viridans* in each. Leukocyte count on May 13 was 7,600. A blood culture on May 12, using penicillinase, was negative.

On May 10 penicillin, 50,000 units, was given every three hours and continued for two days without obvious benefit. He continued to have a remittent fever as high as 103.6° F., but complained only of mild headache and cough. On May 12, streptomycin, 0.5 gm. every six hours, was begun and continued for six days.

His fever promptly subsided and his symptoms disappeared, although the signs of consolidation of the right lower lobe disappeared only gradually during the next week.

Chest roentgenogram on May 10 revealed pneumonic infiltration just above the right diaphragm. Roentgenogram on May 14 showed considerable clearing. Cold agglutinin titers on May 17 and May 23 were less than 1:4.

COMMENT

The cases presented here were not exhaustively studied. Control studies were not done. In a disease with such a variable course, controls are difficult to evaluate in a small series of cases. It was the opinion of several observers, however, that the improvement following streptomycin was so striking in each case that there could be little doubt that it had produced a specific effect on the disease. More control studies would be needed to prove definitely the therapeutic effect of streptomycin in atypical pneumonia. The results in these cases appeared to be uniformly good, and it is felt that further trial of streptomycin in atypical pneumonia is warranted.

SUMMARY AND CONCLUSIONS

Ten cases of primary atypical pneumonia of unknown etiology treated with 2 gm. streptomycin daily are presented. Five cases are given in detail.

An improvement was noted in each case, with prompt subsidence of fever and disappearance of symptoms.

Streptomycin, in addition to aureomycin and chloromycetin, appears to be a specific treatment for atypical pneumonia.

BIBLIOGRAPHY

1. Kneeland, Y., Jr., Rose, H. M., and Gibson, C. D.: Aureomycin in the treatment of primary atypical pneumonia, *Am. J. Med.* 6: 41, 1949.
2. Shoenbach, E. B., and Bryer, M. S.: Treatment of primary atypical non-bacterial pneumonia with aureomycin, *J. A. M. A.* 139: 275, 1949.
3. Wood, E. J.: Atypical pneumonia treated with chloromycetin, *Lancet* 2: 55, 1949.
4. Finland, M., Collins, H. S., and Wells, E. B.: Aureomycin in the treatment of primary atypical pneumonia, *New England J. Med.* 240: 241, 1949.
5. Pulaski, E. J., and White, T. T.: Streptomycin: report of its clinical effects in 44 cases treated for various infections of the respiratory tract, *Arch. Int. Med.* 82: 217, 1948.

A SOURCE OF ERROR IN THE DETERMINATION OF BASAL METABOLIC RATES BY THE CLOSED-CIRCUIT TECHNIC *

By HAROLD N. WILLARD, *Claverack, New York*, and GEORGE A. WOLF, JR.,
New York, New York

IN the course of studying mechanisms of dyspnea with the closed-circuit Benedict-Roth type spirometer, we were impressed with the effect which changes in the midposition of the chest had upon the slope of the spirogram. This possible source of error attracted the attention of Greene and Coggeshall¹ and was also mentioned by Buckingham and Roth.³ Further work by Greene,² however, minimized its clinical importance by showing that when changes in the midposition of the chest did occur during the tracing, they could be detected in most instances by observing the subject's respirations or by noting irregularities in the base line of the spirogram.

The purpose of this study was to determine the effect of slowly changing midposition of the chest upon the apparent metabolic rate as determined by the closed-circuit spirometer method, and to evaluate its clinical significance.

METHOD

Studies were made on trained subjects and on selected patients. A closed-circuit Benedict-Roth type spirometer with a five liter drum was used. After the drum was filled with oxygen, its movement was recorded by an ink-writing kymograph on a standard graph paper calibrated in calories per hour. Calculations were made using the Boothby and Sandiford modification of the DuBois standards, with corrections for temperature, barometric pressure, and surface area. The spirometer used was also calibrated so that the slope of the spirogram could be interpreted in terms of volume of gas as well as in calories per hour.

To demonstrate the effect of change in midposition of the chest on the slope of the spirogram, trained subjects altered their chest volume slowly during six and 12 minute tracings. This was done in two ways. First, the subject filled his chest and was connected with the closed-circuit spirometer. During the tracing he breathed at his usual tidal volume and rate, but with each breath he allowed a slight amount of the supplemental air to escape from his chest, so that the chest volume was slightly less at the end of each expiration. Therefore, by this mechanism, part of the supplemental air was shifted in the closed-circuit from the chest into the spirometer drum. Second, the reverse procedure was carried out. The subject emptied his

* Received for publication December 2, 1948.

From The Department of Medicine, Cornell University Medical College and The New York Hospital.

chest prior to being connected to the spirometer, and then increased his chest volume by small increments with each breath, thus shifting gas from the spirometer drum into the chest.

To produce experimentally changes in chest volume so that methods for their detection could be studied, the following procedure was used. With trained subjects, two facts were established: (1) Before each experiment, the resting oxygen consumption of the subject was measured. This was done first with the closed-circuit spirometer and immediately after with the Tissot-Haldane gas analysis technic. Comparison of the results showed that, in trained subjects, the two methods gave values which checked closely, and so the slope of the spirogram could be taken as a true reflection of oxygen consumption. (2) Spirograms were then performed in which the rate of removal of gas from the spirometer drum was controlled by drawing a line of desired slope on the kymograph paper prior to the start of the experiment. An observer, by coaching the subject, controlled the rate of change in the subject's chest volume by telling him to stop in expiration each time the kymograph pen touched this line. Thus any desired rate of change in chest volume could be obtained. The amplitude of the change in chest volume will be equal to the difference between the slope reflecting oxygen consumption alone, and that reflecting oxygen consumption plus chest volume change, i.e. the difference between the slope of the control spirogram and the slope of the spirogram observed during coaching. Thus, if the subject decreases his chest volume during the tracing, the slope of the coached spirogram will be lower than the control, and, conversely, if the slope of the coached spirogram is steeper than the control, the chest volume will have increased during the tracing.

The next step was to find some simple method by which changes in chest volume could be detected as they occurred in trained subjects and patients during the determination of the basal metabolic rate, for these changes may occur without producing irregularities in the baseline of the spirogram or in the subject's respirations. A spring pneumograph was used with an ink-writing attachment that recorded on the kymograph paper simultaneously with the spirogram. The pneumograph was attached lightly around the chest at the nipple level in order to record changes in chest circumference. Occasionally, this technic recorded some change in chest circumference, but it was unreliable because chest volume may also change considerably without a recordable change in circumference. Spirograms were then made with pneumographs placed around the abdomen as well as the chest, in an effort to record changes in the midposition of the diaphragm. It was found, however, that only large changes in chest volume were detectable in most instances.

In an attempt to demonstrate that a change in chest volume could occur without being recorded by the pneumographs attached to the chest and abdomen, the following experiment was devised. After obtaining the slope

of a curve indicating resting oxygen consumption in a trained subject, the subject was placed on a tilt table. During a six-minute spirometer tracing he was slowly and progressively tilted head up at the rate of 5 degrees a minute; the abdominal organs exerted more and more pull on the diaphragm, the midposition of the diaphragm lowered, and the chest volume increased. This was substantiated by the fact that the slope of the spirogram, done while tilting, was steeper than that of the resting spirogram. However, the attached pneumographs revealed no significant change in the circumference of the chest or abdomen. In a further effort to measure chest volume, determination of complemental airs at the beginning and end of the spirometer tracing was tried on trained subjects. After being connected with the spirometer, the subject was told to take the deepest possible inspiration after a normal expiration, and then repeat the maneuver at the end of the tracing before being disconnected. The method was tried on patients but, because of lack of coöperation or understanding by the patients, it was discarded as an inaccurate indicator of change in chest volume.

Finally, selected patients were studied by using the closed-circuit spirometer technic and comparing the results of this method with those obtained by the Tissot-Haldane gas analysis technic. These patients came to the laboratory in the morning under basal conditions. After a 15 minute rest, two six-minute tracings were obtained by the closed-circuit spirometer technic. Then the patient was connected to a Tissot open circuit spirometer and the expired air was collected for 12 minutes. An aliquot of the collected gas was then analyzed for oxygen, and the oxygen consumption and BMR calculated.

RESULTS

Using the Benedict-Roth closed circuit spirometer, trained subjects could voluntarily produce tracings representing apparent metabolic rates of from 96 per cent lower to 100 per cent higher than their true oxygen consumption. These results were obtained by slowly decreasing or increasing the volume of supplemental air in the chest during the tracing. Figure 1 shows duplicate falsely low six-minute tracings done by a trained subject; without coaching of any kind, they checked within 2 per cent and were considered satisfactory by trained BMR technicians. The calculated metabolic rate as determined from these tracings was 40 per cent lower than the normal for that subject.

That such an error can also occur in a 12-minute tracing is shown in figure 2. The baseline in this figure is regular, for the subject was being coached, and the rate was again 40 per cent below the subject's normal. In both instances the performance of the tracings was done with ease and did not result in any discomfort. Indeed, it was possible to make six minute tracings which indicated absurd apparent metabolic rates as low as minus 96 per cent without a great deal of difficulty. Furthermore, on close

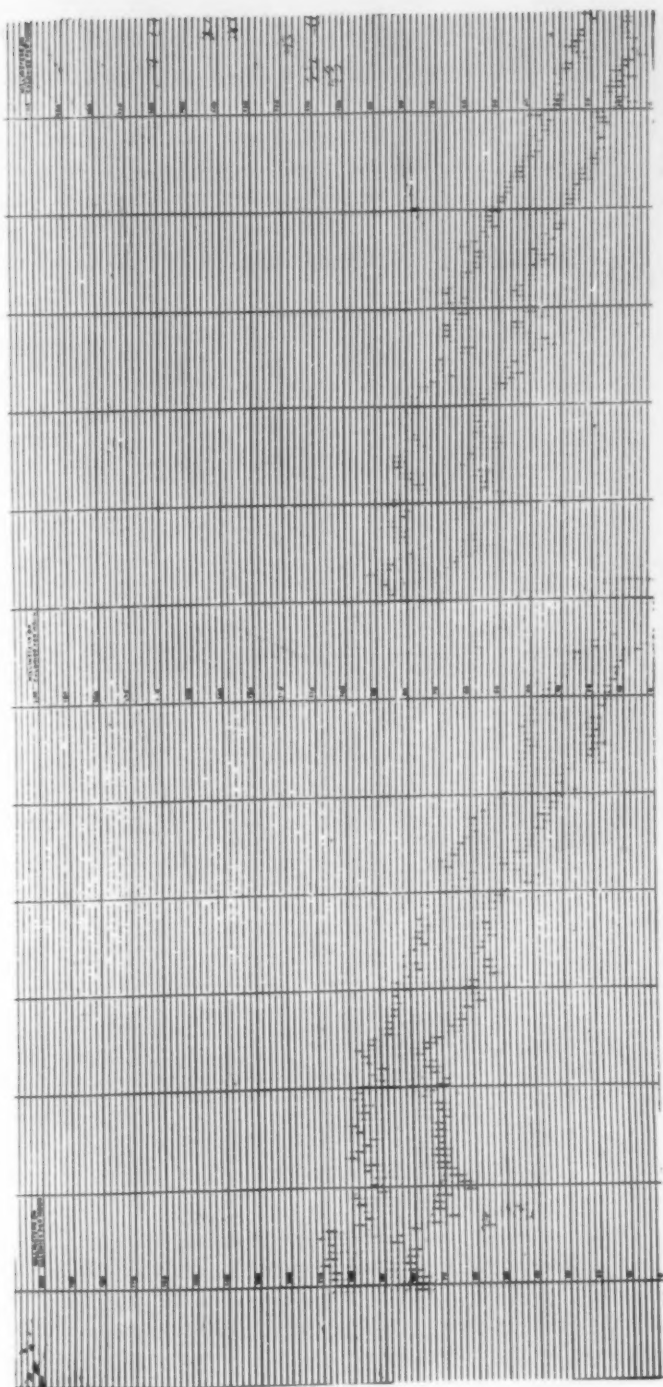


FIG. 1. Duplicate six minute spirometer tracings.
Falsely low.

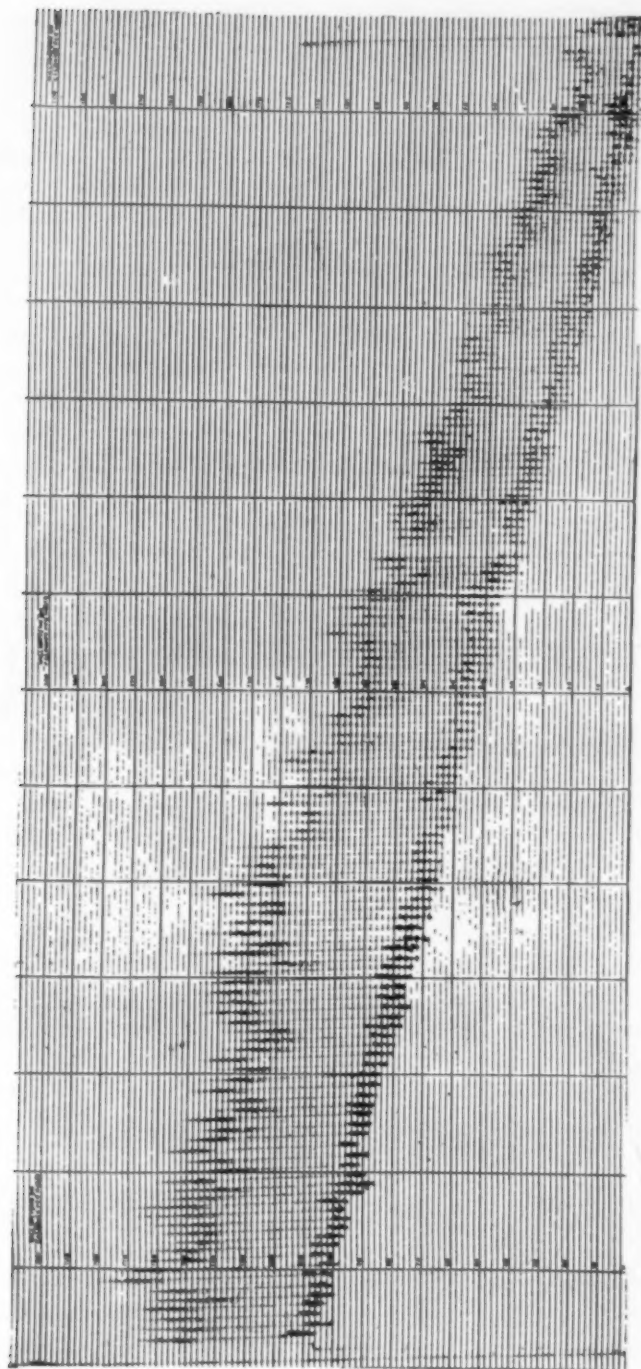


FIG. 2. Twelve minute spirometer tracing.
Falsely low.

scrutiny of the subject's respirations while performing moderately low apparent metabolic rates, no abnormalities could be detected.

A simple calculation emphasizes the ease of production of such tracings. If we postulate a patient whose basal heat production is 54 calories per hour with a BMR of 0, and if the correction factor for barometer reading and temperature is .900, the baseline of the spirogram would rise to the 60 calorie per hour mark in six minutes. Now let us suppose that the same subject slowly increases his chest volume during the tracing, and in so doing

TABLE I

	Lab.	Pneumo.	Diff.
1. G. W.	+ 4%	+ 4%	0%
2. H. L.	- 2%	- 1%	+ 1%
3. A. P.	-13%	- 4%	+ 9%
4. D. B.	- 1%	+12%	+13%
5. R. T.	- 4%	- 3%	+ 1%
6. J. S.	+29%	+60%	+31%
7. C. F.	-16%	+ 2%	+18%
8. C. Y.	+ 8%	-36%	-44%
9. C. F.	+ 9%	+21%	+12%
10. I. S.	- 6%	-11%	- 5%
11. J. R.	- 4%	- 2%	+ 2%
12. F. L.	+21%	+17%	- 4%
13. G. E.	-19%	-25%	- 6%
14. R. C.	- 4%	+16%	+20%
15. E. I.	+ 4%	+13%	+ 9%
16. G. E.	-10%	+27%	+37%
17. B. S.	-18%	-11%	+ 7%
18. M. P.	-15%	- 7%	+ 8%
19. N. C.	- 8%	- 4%	+ 4%
20. M. D.	+ 2%	+ 2%	0%
21. R. S.	-23%	+21%	+44%
22. H. C.	-23%	-23%	0%
23. G. D.	+ 5%	+12%	+ 7%
24. G. S.	- 9%	- 9%	0%
25. J. J.	+ 2%	+ 2%	0%
26. G. P.	+ 4%	+35%	+31%
27. L. T.	+ 9%	+17%	+ 8%
28. D. L.	+ 1%	+20%	+19%
29. D. P.	-11%	+ 9%	+20%
30. J. G.	+ 5%	+38%	+33%

Lab. Apparent metabolic rate as shown by routine laboratory tracings.

Pneumo. Apparent metabolic rate after pneumograph was applied.

Diff. Difference between results found by routine tracings and tracings with pneumograph attached.

the baseline of the spirogram rises to the 75 calorie per hour mark in six minutes. The latter tracing would therefore be falsely high by 15 calories per hour. By calibration of the spirometer drum, it is found that removal of 21 c.c. of gas from the spirometer drum moves the recording pen up one calorie-per-hour line on the kymograph paper. Therefore, to perform the tracing which is falsely high by 15 calories, the patient increased his chest volume by 15×21 c.c., or 315 c.c. of gas. If he were breathing at the rate of 16 a minute during this six minute period, he only increased his chest

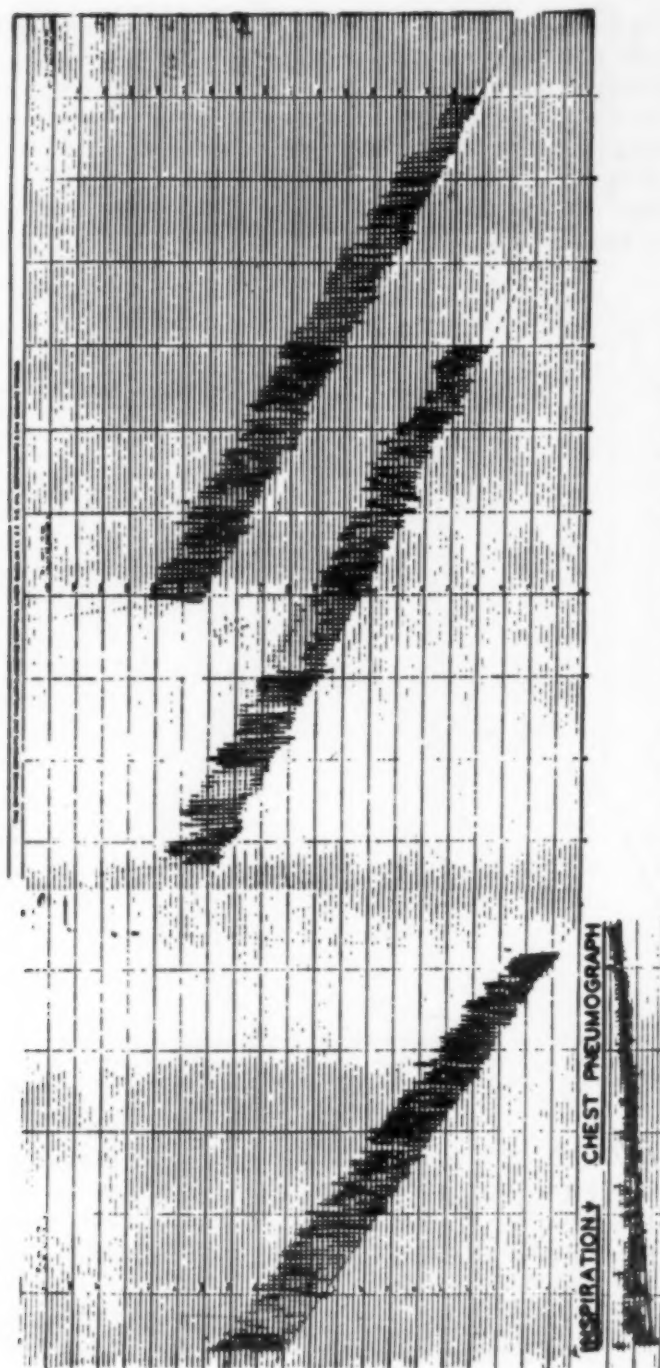


FIG. 3. Falsely high metabolic rate caused by increase in chest volume.

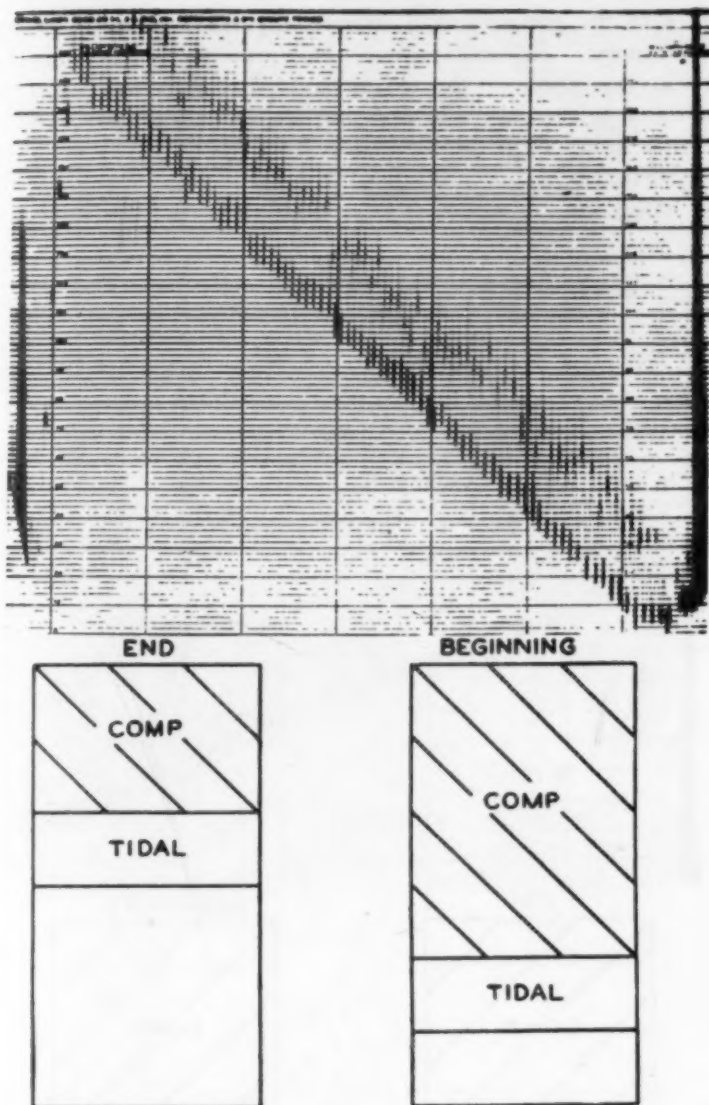


FIG. 4a. Falsely high metabolic rate.

volume $315/16 \times 6$, or 3.3 c.c. with each breath. Since calculating the metabolic rate from the higher slope gives a value of plus 25 per cent, it can be seen that he was able to increase his apparent metabolic rate markedly by this relatively small change in chest volume.

Thirty random patients coming to the basal metabolism laboratory were studied with the chest pneumograph as a measure of possible changes in chest volume. After the routine tracings were completed, a third tracing

was done with the pneumograph strapped lightly around the chest at the level of the nipples. In most instances, this procedure caused a considerable alteration in the slope of the spirogram. Table 1 shows the apparent metabolic rates before and after applying the pneumograph. The cause of this change was not clear, but it was evident that a slight modification of the test procedure of determining the BMR, including the constricting effect of the pneumograph about the chest, seriously interfered with the accuracy of the test.

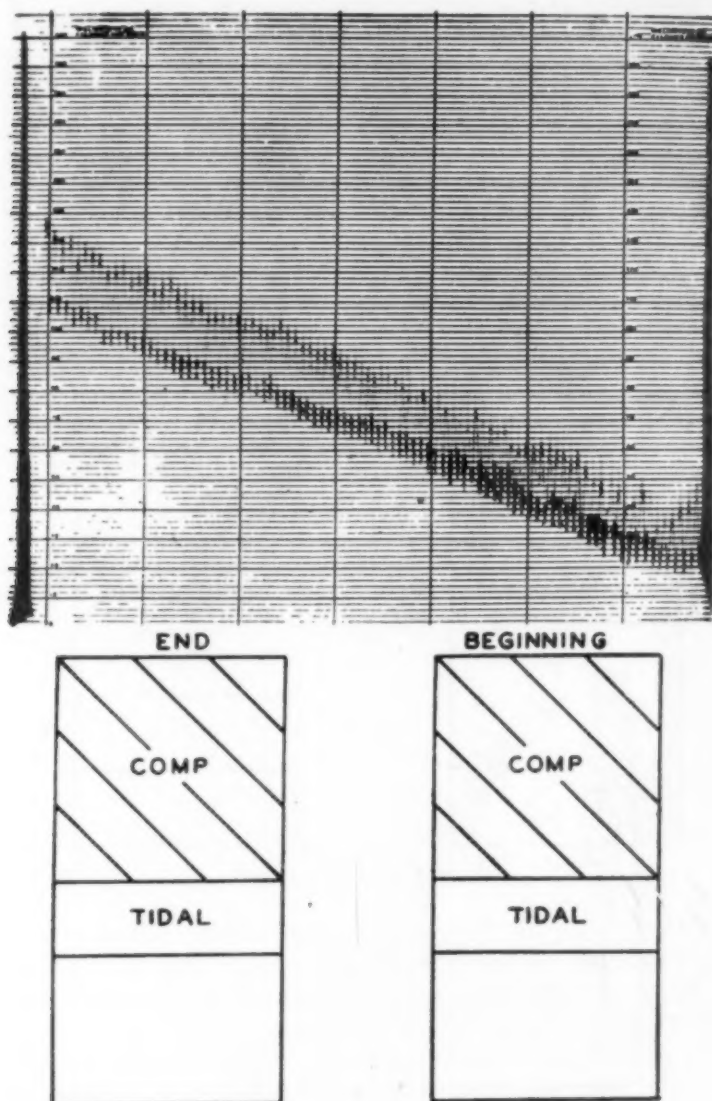


FIG. 4b. Normal metabolic rate.

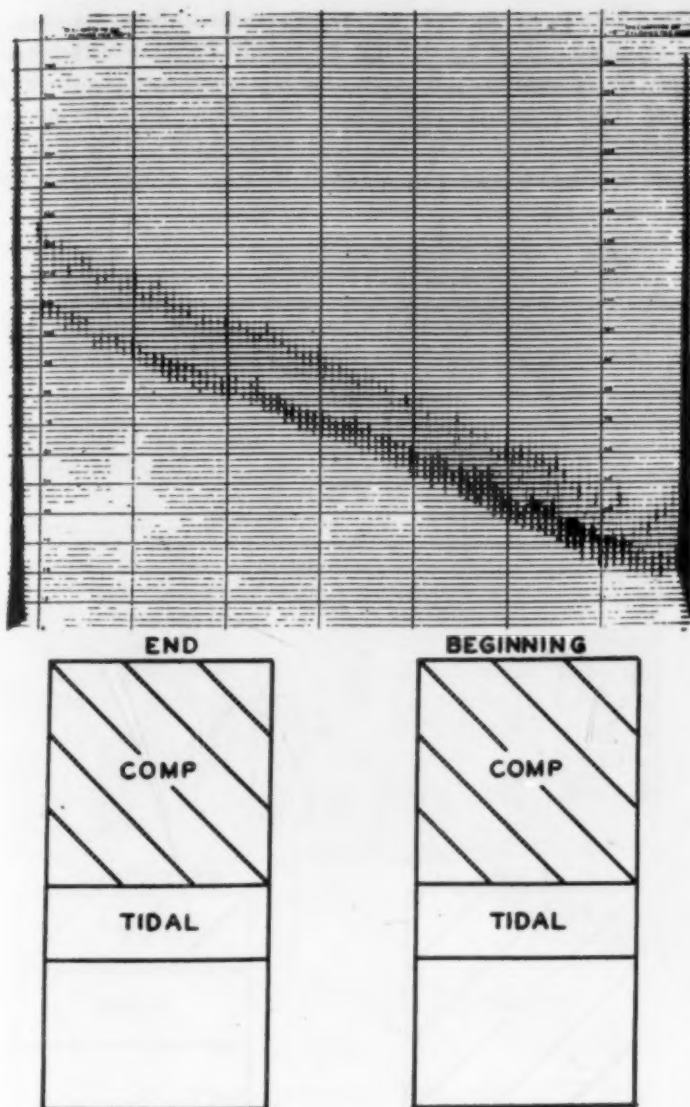


FIG. 5a. Normal metabolic rate.

In spite of this, the observations were most rewarding in one instance, where a graphic demonstration of change in chest volume as recorded by the spring pneumograph, and its effect on the spirometer curve, were observed. This patient was a 48 year old white male. He had a toxic nodular goiter and congenital heart disease with mild dyspnea but without signs of congestive heart failure. The two routine tracings done by the technician were satisfactory, checked within 4 calories per hour, and indicated a BMR of plus

30 per cent. The pneumograph was then attached about his chest and the spirogram repeated. During the test he slowly became uncomfortable and progressively more anxious. The resultant tracings are shown in figure 3. The slope of the tracing farthest to the left, done with the pneumograph attached, indicates an apparent metabolic rate of plus 60 per cent, but the pneumogram by its declining slope reveals that the increase was due to pro-

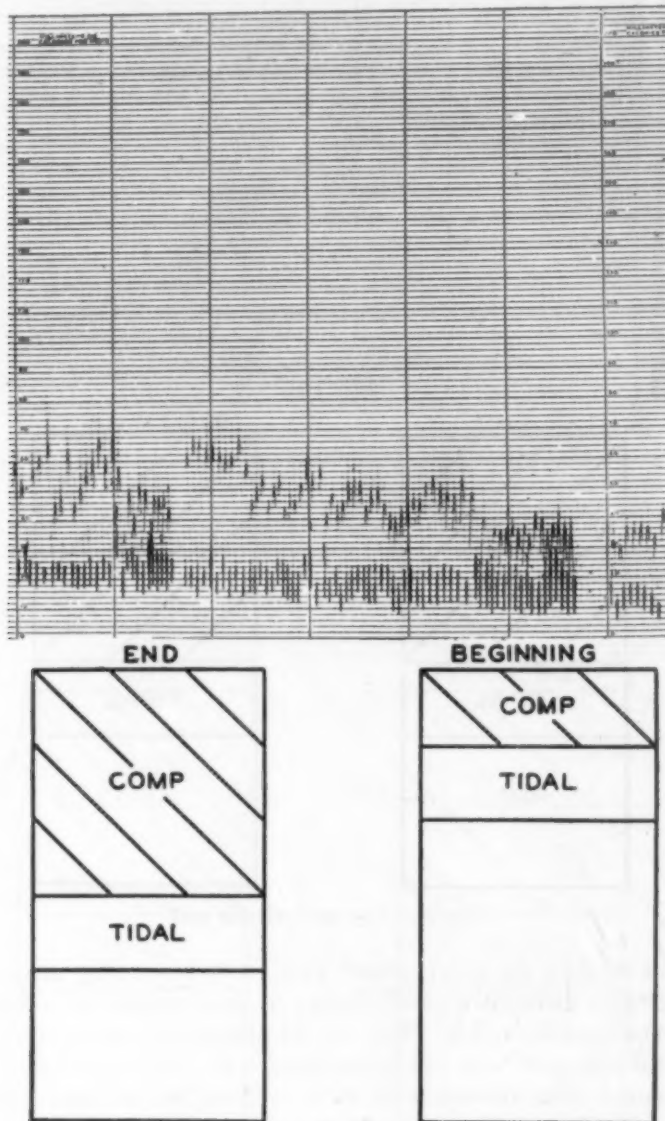


FIG. 5b. Falsely low metabolic rate.

gressive expansion of the chest during the tracing with resultant increase in chest circumference and shift of gas from the spirometer drum into the chest. Noteworthy is the fact that closest inspection of the spirogram does not reveal the source of error, for the expiratory baseline is quite straight.

In trained subjects, complementary air determinations demonstrated the changes in chest volume which occurred during falsely low and high tracings. In figure 4 a falsely high apparent metabolic rate is contrasted with the subject's normal tracing. The dark spikes at the beginning and end of the

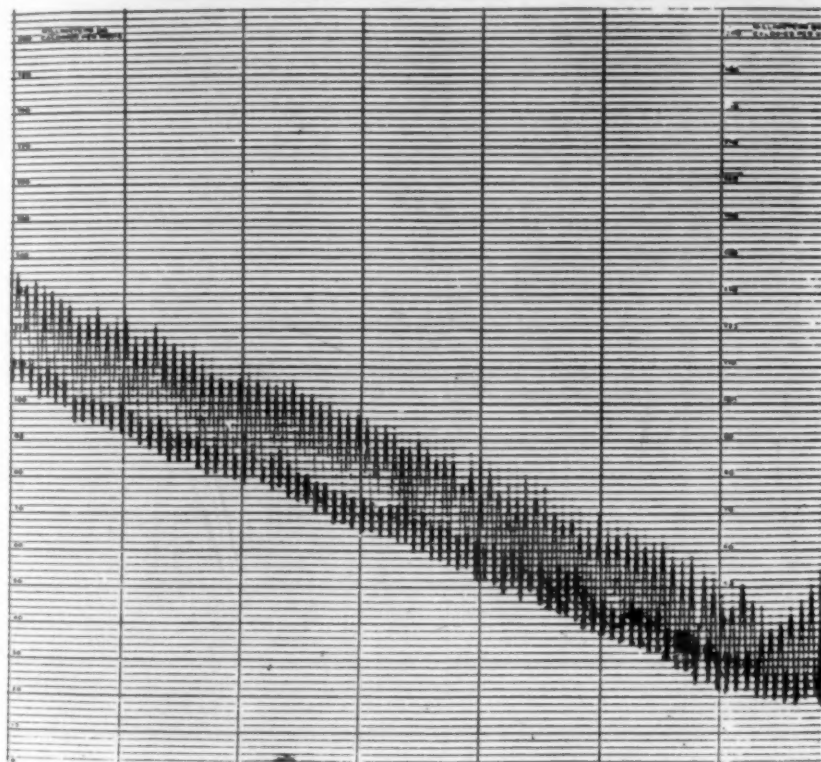


FIG. 6a. Normal metabolic rate.

tracings represent the complementary airs. It can be seen that in the normal the amplitudes of the initial and terminal spikes are equal, indicating that no change in chest volume occurred during the test. In the falsely high tracing, the subject started with a relatively empty chest, and therefore the complementary air was high. During the tracing he slowly filled his chest, and consequently at the end he was able to take in little extra air, and the complementary air was low. In figure 5, which shows a falsely low apparent metabolic rate contrasted with the normal, the reverse is true. The dif-

ference between the volumes of complementary air at the beginning and end of the tracings is equal to the difference between the volume of the true and the apparent oxygen consumption.

Figure 6 illustrates, with the aid of complementary air measurements, increasing chest volume occurring due to lowering of the midposition of the diaphragm, with consequent altering of the slope of the spirogram. In this figure the normal resting metabolic rate of the trained subject is shown on the left. The tracing on the right was done as the subject was being

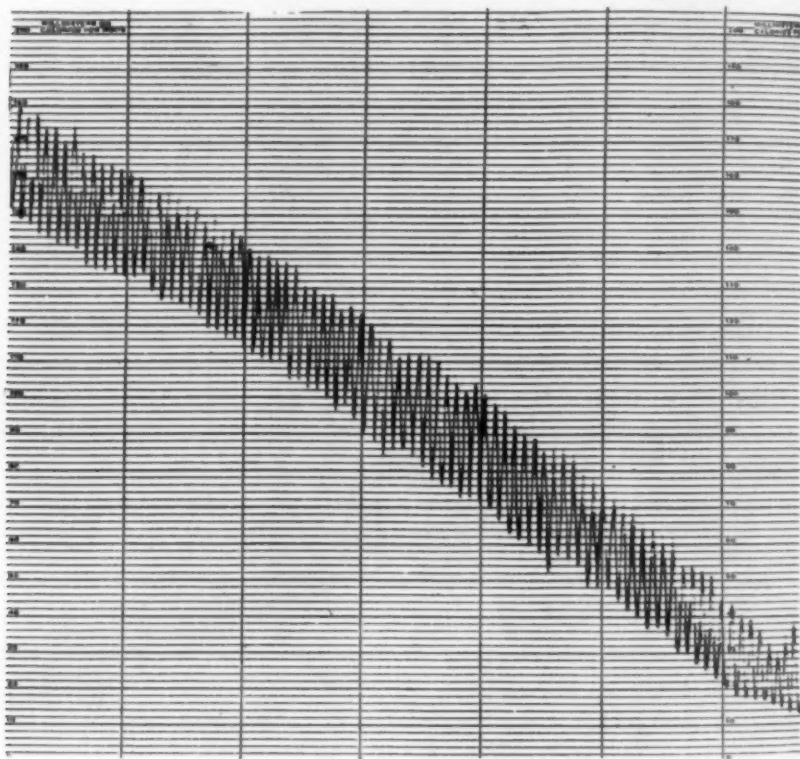


FIG. 6b. Tilt 5 degrees/minute.

Falsely high metabolic rate.

tilted slowly and progressively head up at the rate of 5 degrees per minute. As the midposition of the diaphragm fell, the chest volume increased, air was sucked from the spirometer drum into the chest, and the slope of the spirogram is therefore falsely high. As in figure 4, the volume of the complementary air at the start of the tracing is greater than that at the end.

Unfortunately, measurement of complementary air as a simple clinical test of change in chest volume is not dependable when used with patients.

The consecutive determination of the BMR of patients by the closed-

circuit spirometer technic and by the Tissot-Haldane technic revealed that falsely low and falsely high metabolic rates do occur occasionally. The results of these determinations are summarized in table 2.

DISCUSSION

The slope of the spirogram in the closed-circuit metabolism apparatus is not a function of the oxygen consumption. It reflects the rate of removal of gas from the spirometer drum only. The rate of the removal of gas is dependent upon the oxygen consumption of the subject and upon the change in the chest volume during the determination. This fact may introduce an error into oxygen consumption determinations by the closed-circuit technic. The source of error should be considered in highly accurate experimental work involving the determination of oxygen consumption in applying the Fick principle to the estimation of cardiac output.

TABLE II

Patient	Closed-Circuit Technic	Tissot Technic	Remarks
C. D.	-10%	-10%	Cholesterol 225
J. A.	-4%	-19%	Cholesterol 220
V. D.	+2%	+3%	Tension state
W.	+44%	+55%	Graves' disease
C.	-4%	-7%	History of thyroid therapy
B.	+12%	0%	Signs of hyperthyroidism
T.	-17%	-18%	History of thyroid therapy
I. B.	-11%	+8%	Neurasthenia
R.	+6%	+31%	Weight loss, sterility
R. R.	+16%	+18%	Overdose of thyroid
A.	+20%	+13%	Anxiety state
D.	-20%	-9%	Anxiety state, cholesterol 258
J. R.	+7%	-2%	Diabetes
F.	-23%	-28%	Anxiety and hypochondriasis
C. W.	-15%	-10%	Thyroidectomy
R. D.	+9%	-1%	Failure to gain weight
A. M.	+40%	+2%	Normal creat. tol. and serum iodine
D. E.	+34%	+25%	Graves' disease

In the routine BMR laboratory this source of error can occur. It should not result in mismanagement of patients if initial BMRs and occasionally subsequent BMRs are not considered sufficient evidence to initiate treatment in the absence of confirmatory clinical signs and confirmatory laboratory tests such as serum cholesterol and creatine excretion studies.

Experience suggests that many young women who are stout or who have slightly irregular menses and who have been found to have on one determination a low BMR, are started and maintained on thyroid substance unnecessarily. It is hoped that a group of such patients can be discovered and studied by the present technics.

It is of considerable importance that striking changes in the apparent metabolic rate can occur when attempts are made to modify the spirometer technic by the attachment of a spring pneumograph to the chest.

Finally, of interest is the fact that increase in chest volume occurred in association with apprehension, mild panic, and dyspnea. The progressive filling of the chest with lowering of the midposition of the diaphragm possibly resulted in impaired ventilatory mechanism of respiration and subsequent intolerable respiratory discomfort.

SUMMARY

Changes in the expiratory position of the chest, occurring during the course of a spirogram done with the Benedict-Roth closed-circuit apparatus, have a marked effect on the slope of the tracing.

When these changes occur progressively and evenly, they are not detectable either as irregularities in the six or 12 minute tracing or by close observation of the subject's respiration.

By its effect on the slope of the spirogram, a change in chest volume may produce either a falsely low or a falsely high apparent metabolic rate.

The use of the chest pneumograph and measurements of complementary air are discussed as simple clinical means by which changes in chest volume could be observed, and are shown to be inadequate.

This potential source of error in the closed-circuit spirometer must be considered in measurements of basal metabolism.

BIBLIOGRAPHY

1. Greene, J. A., and Coggeshall, H. C.: Clinical studies of respiration, influence of determination of basal metabolism on respiratory movements in man, and effect of these alterations on calculated basal metabolic rate, *Arch. Int. Med.* 52: 226, 1933.
2. Greene, J. A.: Frequency and significance of changes of expiratory chest volume during routine measurement of basal oxygen consumption, *J. Lab. and Clin. Med.* 21: 1231 (Sept.) 1936.
3. Roth, P., and Buckingham, P. E.: The criteria of a dependable basal metabolic report, *Am. J. Clin. Path.* 9: 79, 1939.

METABOLIC CRANIOPATHY: A REVIEW OF THE LITERATURE WITH REPORT OF A CASE WITH DIABETES INSIPIDUS *

By SIDNEY DANN, M.D., *Brooklyn, New York*

SHERWOOD MOORE (1935, 1936)^{30, 31, 32} was responsible for reviving interest in a syndrome (or group of syndromes) which had received only scant attention during the previous century and a half. It is the purpose of this paper to review the literature to date on this protean syndrome and to give a detailed report of a case with an unusual variant—diabetes insipidus.

HISTORY OF DISEASE AND REVIEW OF LITERATURE

Hyperostosis of the frontal bones (henceforth to be termed HFI) associated with virilism and obesity in a 75 year old female was first described by Santorini and Morgagni in 1765. During the following 150 years occasional reports appeared in the literature, but many of the descriptions included entities which, according to present day criteria, would not be acceptable either pathologically or clinically as true examples of Morgagni's syndrome. Lobstein (1833), Rokitansky (1850), Hauff (1844), De Lee (1913), and Williams (1923) described lesions, and some of their descriptions would be acceptable today. Undoubtedly, this lesion antedated its first official description; Henschen has reported typical findings in skulls found in early Nordic graves. Moreau³⁴ reviewed the autopsy findings in a priest executed for quadruple murder in 1785 and described the hyperostotic changes in the skull; he tells the story of the priest, who had been a cultured and gentle individual but who evidenced marked mental and emotional changes prior to the slayings. Numerous pathologic and anatomic studies followed; although clinical data were scanty, these studies served the useful purpose of clarifying the details of the pathology and of excluding other entities which hitherto had been confused with HFI. Obviously, the lack of adequate roentgen-ray diagnostic facilities impeded more frequent recognition of the syndrome. In 1928, R. M. Stewart³³ reviewed the subject of hyperostosis, added a case of his own (which had been autopsied 15 years earlier), and added psychosis to the list of symptoms associated with the bony changes in the skull. In the same year, Grieg³⁶ described thickening of the internal table of the frontal bone as being quite common in elderly females and not associated with a definite clinical picture. However, his report was based largely on museum specimens and clinical data were scanty. In 1930, Ferdinand Morel³⁵ published the first report of the syndrome diagnosed in a living subject. His material included four autopsies performed per-

* Received for publication July 6, 1948.

From the Medical Service, Cumberland Hospital, Brooklyn, N. Y.

sonally, the protocols of 11 other cases, and a living subject, an 81 year old female who had been confined to a mental institution for 30 years. Morel emphasized the endocrine as well as the neuropsychiatric symptomatology. In his cases, hyperostosis was associated with obesity, headache, neurologic abnormalities, and mental disturbances. Postmortem examination revealed peculiar changes in the wall of the third ventricle, characterized by an increase in the pigment and the fat. He attributed these changes and the hyperostosis to a common etiology.

Van Bogaert (1930)³⁶ reported the case of a 66 year old female with obesity and progressive mental deterioration; her blindness was presumed to be due to pressure on the optic nerves as they passed through the orbital foramina. Schiff and Trelles (1932)⁴⁹ described the case of a 60 year old female who, following an accident resulting in cerebral concussion, experienced headaches, convulsions and personality changes; she was described as having a "neurosis" and intellectual slowing. There was, in addition, a disturbance of gait and equilibrium. She was obese. There was hypercalcemia.

Early reports of the roentgen-ray changes in hyperostosis were those of Naito (1924), Schuller (1924), Casata (1926), and Leri and Cattentot (1926).

In 1935 and 1936, Sherwood Moore began an extensive search for what he originally conceived to be the cranial manifestations of melorheostosis leri. At the time he undertook his project he was unaware of Morel's thesis and, when he recognized the syndrome to which he gave the title "metabolic craniopathy," he freely acknowledged Morel's priority in the field. Despite an intensive search of the literature, he was able to find only three case reports made during the lifetimes of the patients—those of Morel, Van Bogaert, and Schiff and Trelles—although he felt it most likely that other cases had been described and had been lost under various diagnoses. He set himself the huge task of reviewing 20,000 roentgen-rays taken on 6,650 individuals over a period of 24 years (1911–1934). His findings will be discussed below.

Because of the frequently vague concepts of the disease and because of the confused nomenclature, it is difficult to estimate accurately the number of cases of HFI that have been reported. Henschen¹⁹ in 1936 was able to cull references to 225 female and eight male autopsies, and added 66 museum specimens of his own. Excluding Moore's cases, he was able to add 28 personally observed cases to the three described in the living subjects prior to that time. Later in 1944,²¹ he was able to describe a total of 269 complete and "defective" cases of Morgagni's syndrome, gathered from his own experience. In 1941 Knies and Le Fever²⁴ estimated that since 1900 something over 300 autopsy and museum specimens had been recorded. Undoubtedly, the true number is much larger. Unfortunately, most cases have not been followed for long periods of time; Knies and Le Fever list

Stewart's⁵³ two year and Eisen's¹¹ 15 month followup as the longest recorded up to 1941. Our case has had a two year follow-up under close observation.

Moore found hyperostosis in 229 cases in his series, or 3.5 per cent of the total. These represented 0.014 per cent of 415,944 admissions during the 24 year period covered. He also examined the skulls of 36 insane patients. Fourteen (42.4 per cent) of these were described as showing the changes of HFI—all of these patients had manifested an indefinite type of psychotic syndrome ("unclassified dementia"). He also examined 660 skulls in the collection of Robert J. Terry, of the Washington University School of Medicine; 1.9 per cent of the male skulls showed HFI, whereas 23 per cent of the female skulls showed similar changes. No significant changes had been noted in the pituitary glands.

In 1936, Carr⁸ reported 17 cases, all in females. The hyperostoses, per se, could not possibly have accounted for the composite picture, and he believed that the HFI was the roentgenologic evidence of an entity, probably metabolic in origin. He offered as proof the high incidence of obesity (64.7 per cent) in his series. No definite conclusions could be drawn from the studies of the basal metabolism; however, the indications were toward the low side. There was an increase of sugar tolerance. Thirteen of the 17 patients had menstrual difficulties; flow was irregular, profuse, or painful. Physical examination of the pelvic organs was noncontributory. The incidence of other symptoms in his series was as follows: headache (82.3 per cent), memory defects (88.2 per cent), menstrual disturbances (76.4 per cent), dizziness (64.7 per cent), mental changes (58.8 per cent), weakness (58.8 per cent), disturbances of vision (41.1 per cent), convulsive manifestations (35.3 per cent), muscular defects (17.5 per cent), and hypertension (11.7 per cent). He emphasized the considerable fluctuation of the symptomatology, but he noted that the headache, weakness, dizziness, and defective memory tended to remain constant. The psychiatric changes in this group also varied widely, but predominantly there was a confusional state with marked irritability and memory defect. Carr was the first to attempt treatment with aminoacetic acid by feeding large amounts of gelatin daily. This was suggested originally by a successful attempt at relieving the weakness in one patient; it was noted that the entire symptom-complex improved concurrently. Carr also noted persistent creatinuria in his patient; this too improved with glycine therapy. Timme,⁵⁵ discussing Carr's paper, stated that the symptoms fell into two groups, dependent on whether the defect resided in the utilization of fat or calcium. The low utilization of calcium resulted in a spastic, overactive state of the neuromuscular system, and such patients would manifest "myotatic irritability, myoedema, and spasms." They are described as spasmophilics, and have convulsions diagnosed as petit mal or even grand mal. He believed the use of calcium was very beneficial.

Eisen (1936)¹¹ reported the case of a 45 year old white female with blindness of one eye and headache, followed shortly after the onset of these symptoms by polyuria, weakness, dizziness, trembling, mental confusion, and a tendency to "witzelsucht." The blood sugar was slightly elevated and there was a small amount of sugar in the urine. Blood calcium was 6.3 mg. per cent. There was no evidence of increased intracranial pressure. Two years later, both the bony changes and the clinical picture showed progression; there had been some degree of mental deterioration. Eisen does not give details about the degree of polyuria, and it is likely that it was a consequence solely of the diabetes mellitus. No attempt is made to classify the type of blindness, a deficiency which is notable in most papers mentioning this symptom. Incidentally, this case received one of the longest periods of observation recorded.

In 1938, de Lehoczky and Orban⁹ reported a case of the Stewart-Morel syndrome in a 72 year old white female. The symptomatology appeared to have had its onset at the age of 61 following a trigeminal herpes zoster (the authors speculate on the possibility that the hyperostosis was the cause of the herpes, and draw a parallel with the bilateral optic atrophy resulting from hyperostosis in Van Bogaert's case). The patient manifested a rhizomelic type of obesity and was nervous and depressed. She suffered from intractable frontal headaches, had an inverted sleep rhythm and impaired powers of memory and attention, and was described as egocentric and hypochondriacal. Roentgen-rays of the skull showed internal hyperostosis of the frontal bones and calcification of the anterior part of the falx cerebri. Blood calcium was normal; there was no polyuria. The roentgen-rays, followed for some time, showed progressive bony changes.

James²² in 1936 described HFI as "an unusual clinical finding" in a 51 year old white female who was seen by him following a head trauma. She was "fat and florid" and resembled a myxedematous individual. She had suffered from severe frontal headaches and giddiness for years. She had frequent fits of depression and was of sluggish mentality, but there was no evidence of psychotic changes. Her skull roentgenograms showed the usual findings, with calcification of the falx cerebri. Large vascular channels in the skull were described as an unusual concomitant finding.

Reider,⁴⁴ in 1938, reported two cases of HFI associated with degenerative brain disease. The first was that of a 55 year old white married woman who, three years prior to her first examination, began to fatigue easily, became nervous, lost 20 pounds, and developed a severe sensory aphasia. With the exception of evidence of previous obesity, the physical examination was normal. Blood pressure was 140/78 mm. Hg. She was disoriented, fluctuated between tears and euphoria, and showed mental deterioration. Examination of the spinal fluid revealed no abnormalities. Basal metabolic rate was minus 10. Air encephalography demonstrated a mild internal hydrocephalus and some suggestion of cortical atrophy. Postmortem brain

changes were found to be typical for Alzheimer's disease (senile plaques, hyalinization of cerebral vessels with perivascular infiltrates). The wall of the third ventricle was normal. The pituitary gland showed nonspecific changes interpreted as "activity." Interestingly, the hyperostoses seen at post mortem were much larger than had been suspected from the roentgenograms taken three months previously and it was thought that progressive changes had occurred. Pressure atrophy of the right frontal and temporal lobes was noted, a phenomenon more frequently postulated than actually described in the literature. It was felt that the hyperostoses did not adequately explain the entire clinical picture; the relationship of HFI to the symptomatology and to true Alzheimer's disease was left in abeyance. The second patient was a 40 year old married female. She had had irregular menses since the age of 11. Following a head trauma at the age of 26, accompanied by a period of unconsciousness lasting several weeks, she had experienced severe headaches for several months and had undergone a marked personality change, becoming malicious, selfish, and compulsive. At the age of 37 she began to complain of marked fatigue. She had petit mal attacks and her memory became defective. Treatment with glycine was ineffectual. Physical, neurologic and laboratory examinations were negative. Air encephalography revealed some cortical atrophy. The bony changes seen on roentgen-ray were typical. Reider does not comment on the relationship between HFI and the head injury, but he claims a definite correlation between the symptomatology on the one hand and the bony changes on the other, and he subscribed to the existence of the syndrome.

Roger⁴⁰ in 1938 reported two cases. One was that of a 57 year old female, definitely obese, who had had parietal headaches for four years "following a fright." These were severe and burning in character and were not relieved by medication. The menopause had occurred at 44. She was depressed. Physical examination revealed only an enlarged heart with a blood pressure of 170/90 mm. Hg and some defect in hearing, apparently accounted for by local pathology. Examination of the central nervous system revealed no unusual findings. Calcium, phosphorus and phosphatase studies were within normal limits. The basal metabolic rate was plus 18. The second case was that of a 52 year old female weighing 220 pounds. She had experienced severe frontal and parietal headaches for three years. She was depressed and emotionally labile. The menses were still regular. Blood pressure was 120/80 mm. Hg. Blood chemistries were normal. Both patients responded to ergotamine tartrate, and Roger related the headache of HFI to true migraine. (It will be noted below that Silzer found this drug useless in his cases.) Roger, too, attributed an important rôle to the pituitary gland in the pathogenesis of the symptoms but could not agree with Pende,⁴¹ who stated that all his cases showed roentgen-ray changes in the region of the sella turcica.

Canavan,⁷ pathologist for the Massachusetts Department of Mental Dis-

case, reviewed 3,250 cases from the state's mental institutions, and 230, or 7 per cent, had hyperostosis. One hundred ninety-one (80 per cent) were females. Seventeen (7 per cent) of those with bony changes manifested the Stewart-Morel syndrome (hyperostosis, obesity and mental disturbances). Thirty per cent showed frontal lobe atrophy. Nine per cent of the pituitary glands were examined histologically and all were normal. Canavan believed that the small percentage of patients with HFI manifesting the Stewart-Morel syndrome made the mere presence of hyperostosis a relatively insignificant diagnostic feature. However, as will be more fully discussed below the bony changes may precede the development of other manifestations of the syndrome by a long period, and the absence of attendant symptoms may mean merely that the syndrome has not yet developed completely.

Silzer⁸² and his associates recorded four cases in relatively young female patients, aged 26, 27, 38, and 40. In two cases the chief complaint was severe headache; glycine relieved this symptom in one patient. Two patients showed emotional changes, intellectual deterioration, and localized neurologic disturbances such as facial weakness, hypesthesia, anisocoria, and so on. The diagnosis of multiple sclerosis had been made in one case. All four patients were obese.

Hemphill and Stengel¹⁸ report a series of cases classified as Morgagni's syndrome from an English mental institution. A short summary of these follows. Case 1 was a 31 year old female who developed symptoms of a rapidly progressing dementia of the organic type, accompanied by some pyramidal signs and slight ataxia. She manifested marked hypersensitivity of the entire surface of the body. There were characteristic signs of meningeal irritation of the lower limbs. Spinal fluid and physical examinations were negative. There was diffuse tenderness of the skull. With the exception of a diffuse hyperostosis, most marked in the frontoparietal regions, no other cause of the symptomatology could be ascertained. Case 2 was that of a well preserved 65 year old woman who had shown morbid suspiciousness for 20 years and, when seen by the authors, had a full blown picture of paranoia. She suffered from severe headaches and the skull was very tender in the frontoparietal regions. There were no signs of increased intracranial pressure. There were symptoms of meningeal irritation and loss of reflexes in the lower limbs. There was a pea-sized exostosis on the saddle of the nose but no other skeletal deformities. Roentgen-rays of the skull showed typical changes. Case 3 was the 32 year old daughter of Case 2. She showed a generalized obesity. There was some dark hair on the upper lip and the cheek but no other signs of virilism. She had a system of delusions remarkably similar to those of her mother. Aside from exaggerated tendon reflexes, the neurologic examination was negative. The blood calcium was 11.5 mg. per cent. For three years prior to admission she had grown steadily more obese. The menses became irregular and scant. She suffered from dizziness and inability to think clearly. Her hyperostoses

were almost identical in degree and distribution with those of her mother. The family history of Cases 2 and 3 is of considerable interest. The husband of Case 2 had been a violent and suspicious individual. Hemphill and Stengel were informed it was learned at autopsy that he had suffered from a bony disease of the skull: they presume this was hyperostosis. Two of the sisters of Case 2 were paranoid, although never institutionalized, and it was believed that one had committed suicide. A third sibling had died in infancy. A nephew of Case 2 had similar skull changes. Her granddaughter (the daughter of Case 3) had marked hyperostotic changes of the skull at the age of 10, and the grandfather described her as "going the same way as her mother." The familial history here is interesting in view of the group described by Knies and Le Fever, and the belief of the latter and of Grollman and Rousseau¹⁷ that hyperostoses are inherited as a dominant trait.

Hemphill and Stengel draw certain conclusions from their series of three cases. A terminal cachexia may mask the obesity usually sought as one of the cardinal signs. Since the mental symptoms are not specific, and even the roentgen-ray diagnosis may present difficulties on occasion, they sought to define some neurologic criteria which might justify the clinician's suspicion of HFI. The only suggestion they could offer was that HFI should be sought as a cause of dural irritation where signs of meningeal irritation exist in the absence of symptoms of acute meningitis. Obviously, this is not highly specific, and it is admitted by the authors that, from the neurologic and psychiatric viewpoints, the disease is poorly defined. Two of the cases manifested a marked fear of being touched, which the authors interpreted as hypersensitivity due to persistent irritation of the dura. They believed this hypersensitivity might have accounted for the similarity to Dercum's disease postulated by Schiff and Trelles in their case. A case of Paget's disease studied by the authors manifested a similar hypersensitivity, and this is advanced as further proof of the dural etiology of the somatic hypersensitivity. This symptom of tenderness of the skin, however, seems limited to the cases described by Hemphill and Stengel. In reviewing the possible mechanisms causing the disturbed mental state, the authors dismiss the possibility of the mere coincidence of the mental symptoms and HFI. They pay only passing tribute to the conception of direct pressure exerted on the frontal lobes (Case 1). They favor an endocrine dyscrasia producing the bony changes and predisposing the individual to a great variety of mental abnormalities. The postmortem changes in Case 1 are discussed. There were diffuse degenerative changes in the frontoparietal cortex which were typical of senility and were only partially explained by direct pressure effects. Degenerative changes involving the hypothalamic nuclei were held to be typical of the disease and probably responsible for the symptoms. There was diffuse fibrosis of the lungs with diffuse calcification; such findings were also suggested in Case 2 on the basis of the clinical picture; the authors speculated on the relation of "calcium retention" to such a pathological development.

It should be pointed out that such findings have not been reported elsewhere and it is most likely that they bear no relationship to the syndrome under discussion. The authors did not feel that the postmortem findings adequately accounted for the clinical diagnosis of dementia and they were unable to explain the neurologic findings.

Knies and Le Fever,²⁴ in an excellent review of the entire subject of metabolic craniopathy, added 28 new cases, five of them males, to the literature. The clinical picture in the male cases did not vary from the usual pattern, and Knies and Le Fever thought that some cases had been excluded from the literature solely on the grounds of sex. Twenty-seven patients were white, one was colored. The ages ranged from 13 to 67, with a tendency for the average age (39.2) to be somewhat lower than previously reported. (However, in Silzer's series the average age was 32.7.) Five patients were below the age of 19. In these cases, only the bony changes were prominent, the rest of the symptomatology being "latent." Three of these were the children of a woman with well marked craniopathy, and all three were characterized as being inept and retarded in school. (The authors suggest routine skull plates as additional diagnostic aids in the study of retarded school children.) Two cases were discovered as the result of routine skull plates taken following an injury, and the writers suggest ataxia or faulty judgment (resulting from the hyperostosis) as possible causes of the traumatic episodes.

Knies and Le Fever emphasized two new concepts in the consideration of metabolic craniopathy: (1) A possible hereditary basis for the disease based on the transmission of a pathologic endocrine (pituitary ?) pattern. They stated that no previous familial cases had been reported, but they were apparently unaware of the report of Hemphill and Stengel published at about the same time. (2) The occurrence of bony changes with mainly latent symptomatology. Eight of the 28 cases fell into this group. This will be discussed below in detail. Knies and Le Fever believed that in some case reports where the symptomatology was linked to trauma, it was very likely that the association was coincidental, a latent hyperostosis being discovered by roentgen-ray studies indicated by the trauma. The claim is made that symptoms in such cases would have developed eventually at any rate, even in the absence of trauma. They, too, believed that the bone pathology and the functional changes are mutually independent and "spring from a common, possibly hereditary, endocrine dysfunction, or from one precipitated by trauma."

The symptomatology presented by their cases was similar in general to the symptomatology of the cases previously described. They believed headache might be precipitated by trauma, just as a nonsymptomatic osteoarthritis might manifest itself for the first time following a trauma. Hyperostosis should be thought of in the consideration of a persistent cephalalgia. Vertigo, obesity and mental changes each occurred in eight cases. Surgical or roentgen-ray castration of the ovaries preceded the development of symptoms

in four cases, and this might point to an ovarian (or pituitary) factor in the precipitation of symptoms. Also reported were weakness, menstrual changes, and increase in the 24 hour urinary output. One case was complicated by extensive multiple myelomas and had frank diabetes insipidus; in the other cases, there is no quantitative statement as to the extent of the increase in urinary output, and comparison with our case is not possible. One patient showed occasional glycosuria without hyperglycemia. A reeling type of ataxia, with unsteadiness of station and gait, was described three times. Significant visual changes and hypertension were each reported twice and epileptiform convulsions once. Degenerative and mildly confusional mental types were noted, and one homicidal psychosis was reminiscent of the much-quoted case of Moreau's Belgian priest mentioned above. In this case, too, quarrelsomeness and incompetency in a previously intelligent individual preceded the murder. No virilism or hirsutism was noted in this series. Pre-roentgen diagnosis was made successfully in some cases, as proved by serial roentgen-rays; however, the writers admit that the roentgen-ray changes still "remain the central diagnostic point of the syndrome." Of interest in this connection, however, is the implication that the symptomatology may antedate, and develop independently of, the bony lesions.

Pneumoencephalography revealed plastic arachnoiditis in one case and distention of the anterior horns of the lateral ventricles in a second. Encephalographic studies have not been carried out frequently in these patients. Reider's report has been abstracted above. Matthew Moore's case,²⁹ reported in 1944, was a 32 year old female who had been diagnosed as a psychoneurotic for many years. She had sustained a minor head injury at the age of eight. For 10 years she had complained of buzzing in her head. For six years she had experienced violent rushing of blood to her head, followed the next day by severe headache, mainly left sided, and sweating. For five years she had suffered from attacks of drowsiness and for the three months prior to examination these attacks had been accompanied by convulsions. There were also impairment of the memory and intermittent double vision. She exhibited a staggering gait. She showed marked swings of mood. She was often negativistic, and tests of intellectual capacity were difficult to interpret. Physical examination revealed a mild proptosis of the left eye, moderate left sided facial weakness of the central type, mild muscular weakness, and suggestive Hoffman of the the left hand. The deep tendon reflexes were exaggerated; there were no pathologic reflexes. Blood pressure was 118/90. Roentgenograms showed frontoparietal hyperostosis interna, with calcification of the falx and a normal but small sella turcica. The blood calcium was 11.2 mg. per cent; blood cholesterol 300 mg. per cent; basal metabolic rate minus 23, minus 10 and plus 2 on three separate occasions. A glucose tolerance test showed 70 mg. per cent for the fasting specimen and 145 mg. per cent and 165 mg. per cent at one-half and one hour, respectively. On three occasions the urinary creatine (24

hour specimen) was 549, 497 and 787 mg., respectively, and the total creatine and creatinine, 603, 1,224 and 860 mg., respectively. She was treated with gelatin and amino acid preparations, and claimed she "felt better"; however, clinically she did not improve and she developed paranoid trends. Pneumoencephalography showed "pronounced cortical atrophy over the frontal and parietal lobes, atrophy of the island of Reil and a moderately advanced internal hydrocephalus with asymmetry of the lateral ventricles." These findings are similar to those seen in cases of dementia paralytica, Alzheimer's presenile degeneration, Schilder's disease, and so on, and it was concluded by analogy that the symptoms manifested by this patient were related to the brain atrophy. Moore believes that metabolic craniopathy is a valid syndrome and that the bony changes are related to the symptoms in either a causal or a concomitant manner. In reviewing Roth's cases⁴⁷ (to be described below), Moore disagrees with his conclusions and reiterates that the symptoms can be definitely associated with the bony pathology. He states that "the cerebral changes occur at a slow and irregular rate to be sure *pari passu* with the metabolic craniopathy and reflect a reaction of the individual tissue to an altered metabolic state." This point is also made by Sherwood Moore and others in a somewhat different fashion: in answer to critics who point to the usually normal blood calcium levels as militating against a disturbance of calcium metabolism, they reply that the long duration and slow (but inevitable) progression of the disease make it likely that the metabolic changes may manifest themselves only intermittently and under such circumstances casual analysis of the blood may be misleading. Matthew Moore states that, if the endocrine manifestations and the craniopathy predominate and there is no overt psychosis or psychoneurosis, then it is called Morgagni's syndrome; if neuropsychiatric disorders develop, the term Stewart-Morel syndrome may be applied.

In 1946, Gilbert¹⁸ reported five cases, two of whom were males. Two were obese females, aged 26 and 33, respectively, complaining of headache and rapid gain in weight. Other symptoms included fainting spells, hyperreflexia, and subjective weakness of an arm and leg. A third patient, a 36 year old female, was stated to have a "psychosis," and later committed suicide. A 39 year old male complained of headache, dizziness, nervousness, fatigability, insomnia, and burning pain in the left arm. A fifth patient was an obese chronic alcoholic with questionable hyperostosis. Diagnoses of psychoneurosis and "psychasthenia" were common in this group.

Andrews¹ described the case of a 45 year old married female with HFI and a history of diabetes mellitus controlled by 40 units of regular insulin. She developed obesity very rapidly along with frontal headaches, and concentric contraction of the visual fields accompanied by pallor of the discs. She began to experience narcoleptic attacks which were diagnosed first as diabetic coma and later as hypoglycemic episodes. Andrews comments on this patient's resistance to insulin (reiterated so frequently by Bartel-

heimer^{3,4}), and states that this was fortunate considering the occasions on which she received intensive treatment for "diabetic coma"; he highlights the importance of making the correct diagnosis in these cases so that at least "one avoids the error of treating the patient for something he does not have."

Brauns⁶ reviewed the skull films taken over a three-year period at the Joseph Pratt Diagnostic Hospital. Of 973 patients x-rayed, 46, or 4.7 per cent, revealed HFI. Ninety-three per cent of the cases were females. Age ranged from 17 to 75, with an average age of 47.5. The most common complaint was headache (63 per cent). It was characteristically nonremittent, and some patients described it as lifelong in duration. Remarkable obesity was found in 12 cases, and significant obesity in 65 per cent. Brauns stated that the most important finding was psychoneurosis, which was diagnosed in 26 of 46 cases. This, he admitted, was possibly due to the high percentage of neurotics entering the clinic. In 16 patients the symptoms were quite severe, most of these patients being incapacitated for productive efforts. No cases of Morgagni's syndrome were found; all were classified as the Stewart-Morel syndrome. Four were hysterics. Twenty (43.4 per cent) complained predominantly of muscular weakness. Hypertension occurred in 34.1 per cent, in contrast to most other series where the percentage did not exceed that of the population at large. In this series the average blood pressure was 186/107 mm. Hg; Brauns believed the association to be significant. Neurologic manifestations were present in nine cases, including hyperactive knee jerk on one side, internal strabismus, nystagmus, and right sided weakness (this patient was discharged with question of brain tumor). One patient complained of transient blindness. Nerve deafness was noted twice. One 32 year old single white female had transient right sided hemiplegia of three days' duration and marked hypertrichosis; no neurologic residua were seen three years later. This has not been uncommon in patients described in the past—multiple sclerosis has usually been diagnosed in such instances. Ataxia and vertigo led to a diagnosis of Ménière's disease in two instances. Six had grand mal seizures. Of seven glucose tolerance tests performed, six showed a diabetic type of curve. In 16 basal metabolic rates determined, the average reading was minus 10. One case with virilism presented evidence of Cushing's syndrome and proved to have a hypophyseal adenoma. More will be said later about the close relationship between Cushing's syndrome and Morgagni's syndrome. Three patients complained of menstrual disturbances consisting of irregularity and oligomenorrhea. One patient, a 17 year old girl, hypertensive (200/100) since the age of 14, had a huge ovarian cyst, low androgen level, and a diabetic blood sugar curve (basophilism was considered a possibility here). One patient had acromegaly; another had acromegaloid features. There was one patient with myxedema, diabetes mellitus, and moderate hirsutism (syndrome of Achard-Thiers). Brauns summarizes the average patient with HFI as a woman, about 45, white, obese, with marked psychoneurotic tendencies, low basal metabolic rate,

hypertension and, possibly, diabetes. Presenting complaints would be severe prolonged headache of the so-called pressure type, muscular weakness, and the usual symptoms of the classical anxiety state.

Gerundo and Helwig¹⁴ report Morgagni's syndrome in a 65 year old white female complaining of fatigue, nervousness, lack of memory, and "indigestion." Headache followed shortly and was accompanied by "memory aphasia." She collapsed suddenly and became confused, excited, and severely aphasic. The entire sequence took place in less than one month. Examination revealed motor aphasia without sensory changes. Blood pressure was 170-130/80 mm. Hg. There were positive Chaddock, Oppenheim and Gordon signs on the left, but no Babinski. Deep tendon reflexes on the left side were exaggerated. Examination of the spinal fluid revealed no unusual findings. The original diagnosis was angiospasm of the intrinsic vessels of the left cerebral hemisphere. There was modest improvement, quickly followed by relapse. Roentgen-ray revealed frontoparietal hyperostosis with unusual thinning of the temporal areas bilaterally. Gerundo and Helwig classify this case as one of Morgagni's syndrome because of the combination of obesity, high blood pressure (?), and mental disorder. There were a few dark hairs on the upper lip, but there was no significant degree of hypertrichosis. The diagnosis in this case might be disputed according to strict definition, but it would undoubtedly fit into the broader category of metabolic craniopathy. The authors postulate the rather ingenious explanation that hypertension causes a decrease of blood flow to the frontal bones and that the resulting anoxemia is responsible for the increased calcification. Not only is the explanation somewhat dubious on physiologic grounds, but also the existence of hypertension itself was not proved in this case. The protocol of the postmortem examination gives no description of the heart, although there is mention that "the organs were explored but no lesion of importance was found." The authors state that the disease is a neuroendocrine disturbance involving the pituitary, the parathyroid and the thyroid gland "undetermined by high blood pressure and arteriosclerosis." They also postulate a possible affinity between Alzheimer's disease and the hyperostosis, but admit the great difficulties encountered in attempting the differential diagnosis during life.

Feiring¹⁵ records an interesting case of an obese soldier of 29 with a proved case of gout (elevated blood uric acid, roentgen-ray changes of the joints) and HFI. The patient had normal sexual development. He was of low intelligence. He showed decreased carbohydrate tolerance, and the blood cholesterol was elevated. Calcium, phosphorus and phosphatase levels were within normal limits. Feiring does not claim any relationship between the gout and the well-defined hyperostosis evident on roentgen-ray. Although in gout a diuresis often precedes an attack, there is no similarity to the constant diuresis that rarely accompanies HFI. The rôle of fat metab-

olism in the pathogenesis is still disputed, but at any rate there is little likelihood that one could relate this to the hyperostotic changes.

McGavack and Reinstein²⁷ report HFI in a 40 year old female with brachydactyly, polyphalangism, and brachymetapodism. She was moronic, quite obese, and manifested microcephaly. She had "been born with small hands and feet." An obese sister and a brother's daughter showed similar changes. The patient showed some hairiness of the skin and had hypertension. Blood calcium, nonprotein nitrogen, cholesterol and glucose were normal. The urine showed a faint trace of albumin and a slight reduction of the copper solution. Glucose tolerance test showed 86 mg. per cent fasting specimen, and half-hour specimens thereafter were 130, 137, 164, 167, and 120 mg. per cent respectively. The basal metabolic rate was plus 2. The authors infer that these anomalous bony changes are related to endocrine growth factors, possibly a hereditary dysplasia. They do not attempt definitely to link the two "endocrine" diseases. At any rate, there appear to be present in this case several of the features of metabolic craniopathy, and it might be safe to assume that the presence of the bony anomalies of the extremities is merely coincidental.

On the Continent, Bartelheimer^{3,4} has been a strong proponent for the frequent occurrence in HFI of an insulin-resistant diabetes, which he terms pituitary, and for the relationship of HFI and Cushing's syndrome. He describes a 32 year old female who developed an insulin-resistant type of diabetes. She had suffered from severe headaches in childhood; later they disappeared. Her mother had had a similar complaint. There were some similarities to Cushing's syndrome: the round, red face, abdominal and axillary striae, diabetes, and hypercholesterolemia. However, the obesity was of a rhizomelic type and not typical of Cushing's syndrome. The blood calcium was normal. Bartelheimer classifies this as a case of Morgagni's syndrome. These cases are of special interest to him because he believes they prove the pituitary genesis of diabetes. Noting that Carr speaks of the *increased* tolerance to carbohydrates that these patients show, Bartelheimer claims that such an increased tolerance often precedes the onset of diabetes. He claims that the presence of the bony changes is helpful in differentiating between the "overfunctioning (insulin resistant, pituitary) type" of diabetes and the "underfunctioning or pancreatic type." Like Henschen and Mellgren, he inclines toward a pituitary genesis of the syndrome, especially emphasizing the activity of the basophils. This will be discussed in detail below. Bartelheimer reports a case of HFI complicated by the Gaisböck type of polycythemia.

Grollman and Rousseau¹⁷ reviewed 1,628 skull plates at the North Carolina Baptist Hospital and found HFI in 78, or 4.1 per cent. This figure is between that of Sherwood Moore and the one given by Eldredge and Holm (25 per cent). Films were usually taken for headache or suspicion of tumor. Forty of these patients gave a typical history. Two

patients without roentgen-ray findings but with a "typical" clinical picture were included. Thus, Grollman and Rousseau agree with those who recognize the syndrome as an entity, and express the belief that these two patients, if followed over a long enough period, will develop bony changes. Only one patient was a male; he suffered from trembling, nervousness, insomnia, periodic blindness, generalized weakness, and bilateral megalomastia. These 42 patients comprised 1 per cent of the general hospital population, and Grollman and Rousseau emphasize the fact that HFI is not a rare condition. Most of the patients were in middle life, but the ages ranged from seven years upward.

Only two patients did not complain of symptoms; of these, one had hypertensive heart disease and uremia, the other chronic cholecystitis. There were no signs or symptoms that might be associated with the bone lesions. Rhizomelic obesity was found in 33. The basal metabolic rate was usually normal. Cholesterol, calcium and phosphorus levels were normal. Two patients had mild glycosuria, controlled by diet. Three were relatively refractory to insulin. Menstrual disturbances, especially amenorrhea, were frequent. Hirsutism occurred in 12; if the patients were obese and hypertensive in addition, Cushing's disease was suspected; one patient underwent an exploratory laparotomy for adrenal disease which was not found. Hypertension occurred in 16 cases, and the writers are strongly convinced the relationship is significant. There were 30 psychoneurotics in the group and, like Eldredge and Holm the authors noted no special type. Four patients had to be institutionalized for depression. Eight were hysterics. There were examples of Jacksonian epilepsy, somnolence, and dizzy and fainting spells. The headache which was present in 19 patients was not amenable to treatment.

CLINICAL DESCRIPTION

The writer has deliberately abstracted the foregoing case reports in considerable detail so that the reader can fully appreciate the variability and frequent vagueness of the symptomatology associated with HFI. It is precisely this variability and vagueness at times that have made many writers reluctant to attach significance to the association of the bony changes and the concomitant symptomatology. Moore³² comments on the "long history of morbidity which is quite indefinite," and elsewhere he states that "a reading of the histories of these cases individually leaves an impression of vagueness, the symptoms related or the physical examination do not fit with any particular pathological state or they might be part of many diseases."³¹ However, in reviewing the cases reported, certain symptoms seem constantly to recur and to be more frequently associated with the bony changes than might be expected at random. And, moreover, there is not much question about the definiteness of the morbidity. Moore comments on the progressive

nature of the disorder; 70 of his first 72 patients were ill, 55 needing hospitalization.

Perkins⁴² divided the clinical features into three groups: first, undoubted endocrine and metabolic disturbances of infundibulopituitary origin; second, changes, particularly of the brain, produced by the local pressure of the hyperostosis (Moore states these effects may in instances actually resemble those of a depressed fracture of the skull); third, the changes of "normal" degeneration of the age group concerned. Other symptoms are probably merely coincidental. However, it is apparent that one would frequently encounter difficulties in attempting to categorize individual symptoms in a given case.

Obesity of the rhizomelic type is common; the breasts are larger and more pendulous than in the common type of obesity. Bartelheimer^{3,4} lays great stock in the absence of the "buffalo" type of obesity as an aid in ruling out Cushing's syndrome; Henschen²¹ does not attach too much significance to this point.

Worry and depression are common. It should be noted that, properly, Morgagni's syndrome applies to the combination of HFI, obesity and virilism, and that the Stewart-Morel syndrome is limited to the combination of HFI, obesity and mental disturbances. From the foregoing it can readily be seen that an individual case will not always fit neatly into one or the other group, and some of the cases briefed in the preceding pages would not stand close inspection from the viewpoint of a purist. For this reason, the term "metabolic craniopathy," introduced by Sherwood Moore, serves a comforting purpose as a catch-all term; even here, again from the puristic viewpoint, it should be recalled that a very small percentage of the cases may not manifest craniopathy until considerably later in the course of the disease and that the term "craniopathy" is inapplicable. On the whole, the Continental group, led by Bartelheimer, Mellgren and Henschen, particularly are mostly concerned with Morgagni's syndrome; the Stewart-Morel syndrome has received much less attention, and there is some reluctance to accept the concept of metabolic craniopathy *in toto*. This should be remembered in the sections to come when their theories and experimental work are being discussed; although we have applied their conceptions to HFI in the broad conception of metabolic craniopathy, their investigations have largely been concentrated on HFI in the limited sense of Morgagni's syndrome.

Headaches are very common and there is often tenderness of the skull. Headaches are usually bilateral (unilateral in our case), and frequently referred to the forehead. Headaches may occur after trauma and years before hyperostoses make their appearance (Henschen, 1945); this phenomenon has been advanced as proof that the pituitary derangement is responsible for the headaches rather than the bony changes themselves, although the rôle of the latter has been an attractive one for many writers. Commonly, there is hirsutism, especially of the chin and the upper lip. There may be mental retardation or deterioration. Patients complain of weakness and fatigability.

Menstrual disorders are often noted. Tinnitus, vertigo and tingling may be annoying. Neurologic disorders of varied types have been seen in association with HFI. There have been reported transient hemiplegias and pareses. There may be seventh nerve weakness, motor speech difficulties, trigeminal neuralgias, loss of the sense of smell, dimness of vision, diplopia, and convulsions which may occasionally run the clinical course of a true epilepsy. Interestingly enough, Moore denies the existence of true hyperostoses in the basal portions of the cranium; nonetheless, he attributes the cranial nerve disturbances directly to the bony changes. There may be lethargy, somnolence, or narcolepsy. The memory may show marked impairment. There may be "neuromuscular insufficiency" (Stewart³³ and Morel³⁵ reported fatty infiltration of the skeletal muscles). Hypertension in most series (for example, Carr's, where it occurred in 11 per cent) is not present in unduly high percentages. However, Pende states hypertension is frequent, especially if there are other signs of "hyperpituitarism." Brauns, too, believes the occurrence of hypertension is significantly related to HFI. Grollman and Rousseau similarly found 16 of their 42 cases of HFI showed hypertension.

More rarely there may be diabetes mellitus and, even more rarely, diabetes insipidus, to which category we believe our case belongs. Although Morel emphasized polyphagia, polydipsia and polyuria in addition to sleep disturbances in his cases, these symptoms were not noted in the 52 cases whose histories were available to Moore.

It is obvious from this list of symptoms that the field for differential diagnosis is quite extensive. Moore points out that some of these cases have been erroneously diagnosed as multiple sclerosis, brain tumor, incipient paresis, pellagra and beri-beri (because of the muscular weakness), neuroses, psychoses, Alzheimer's or Pick's diseases, cerebral arteriosclerosis, and so on.

Moore states that the basal metabolic rate in these patients is lowered, whereas the sugar tolerance is increased. Blood calcium and phosphorus levels are within normal limits: some cases have shown slightly elevated calcium levels (12 to 15 mg. per cent). Schneider found hypercalcemia and alteration of the pH. In Moore's series the syndrome occurred 98 per cent of the time in females. In the series of Schneeberg et al.,⁵⁰ 88.6 per cent of the cases were found in females. In general, the bony changes (and the clinical syndromes) occur in middle aged and elderly females. Knies and Le Fever reported a higher percentage of males, several of whom had sustained head injuries. The average age in Schneeberg's series (summarizing 657 cases from the literature) was 46. The youngest patient in Moore's series was 18; the youngest in the series of Knies and Le Fever²⁴ was 13. The degree of bony change is not related to age. Moore states there is no racial or familial predilection; however, Knies and Le Fever²⁴ and Hemphill and Stengel¹⁸ do report familial trends, but these cases are in a minority. Of Moore's³² cases 4.4 per cent had associated thyroid disease, usually "in-

sufficiency"; Casata reported a case complicated by hyperthyroidism. Moore had three cases of frank acromegaly; several of the other cases are reported as possessing "acromegaloid features." Many other endocrine and neoplastic entities have been described occurring in patients with hyperostosis; the relationship is probably fortuitous in most instances, but a few writers believe a causal relationship exists, especially when the associated lesions involve the pituitary-hypothalamic region. The German and Scandinavian writers, Henschen^{20, 21} particularly, see a close relationship to Cushing's disease and adrenal disturbances. Adiposogenital dystrophy has been found. Moore and others describe tumors of the hypothalamus and of the pituitary. Knies and Le Fever recorded previously unreported associated pathology: carcinoma of the thyroid with cranial metastases; multiple myelomas with extensive cranial invasion, including the sella (this patient had diabetes insipidus). Such lesions are undoubtedly purely coincidental.

In general, the earlier writers claimed they found stigmata of underactivity of the pituitary gland (possibly after a period of overactivity, as might be indicated by the acromegaloid features). The work of Henschen and Mellgren²² implicating basophilic *overactivity* will be discussed in detail below.

In summary, because of the widespread symptomatology, systemic and endocrine in nature, Moore felt justified in grouping the entire complex under the term "metabolic craniopathy," with which we may profitably replace the older clinical terms such as Morgagni's syndrome and the Stewart-Morel syndrome, and the purely morphologic descriptive terms, such as calvarial enostoses, calvarial hyperostoses, and intracranial osteophytes.

RADIOLOGIC CRITERIA

Moore^{30, 31, 32} was the first to classify carefully the roentgen-ray changes seen in HFI. In the 6,650 individuals whose roentgen-rays he reviewed, he found 229 cases of HFI, or 3.5 per cent. He described four types of skull changes: (1) Hyperostosis frontalis interna: 96 cases, or 1.44 per cent of the total series. This is "newly formed cancellous bone dependent from the inner table of the squama frontalis." This new bone is nodular or sessile. It does not extend past the coronal suture posteriorly. Occasionally it reaches the orbital plate of the frontal bone. The changes do not appear in the vault. This change may be combined with calcification of the falx cerebri. These changes have a progressive development. The sulcus of the superior longitudinal sinus is spared. (2) Less common is the nebula frontalis. This was present in 76 cases, or 1.14 per cent of the total. This involves the diploë, leaving the tables of the skull untouched and without projections from the surfaces. It is often difficult to determine. Henschen (1944) considers this type anatomically questionable. (3) Hyperostosis calvariae diffusa. Here there are a diffuse thickening of the vault and an increase in the density of the diploë out of proportion to the increase in its volume. This type is also difficult to determine. It occurred in 40 cases, or 0.5 per

cent. (4) Hyperostosis frontoparietalis resembles the second and third types, except for its location. It is possibly a step in the development of the third type. The maximal thickening is at the central parts of the squamous portions of the frontal and parietal bones. This is the least definite of the types and the rarest, occurring in 17 cases, or 0.3 per cent.

To these four types, Knies and Le Fever²⁴ added a fifth—thinning of areas of the frontal bones associated with one of the types described above. Three of their 28 cases fell into this category. Other writers, too, have noted thinning of the bones of the vault associated with the clinical picture of metabolic craniopathy. Knies and Le Fever were not able to classify their 28 cases as rigidly according to type as did Moore, and they believed some overlapping of types was usually present. They considered this to be academic; the clinical picture was not dependent on either the type or the extensiveness of the bony changes.

Moore points out that in all types there is bilateral symmetry in extent and degree of change. There is no change in the outer table, which remains regular and smooth. Moore believes this feature to be significant because the increased volume of bone under these circumstances has to be accommodated at the expense of the capacity of the cranial cavity, and this is thought in part to be responsible for the symptomatology. He believes all four types have fundamentally the same etiology, although they are morphologically distinct; the similarity is also indicated by the closely related clinical phenomena. He also emphasizes that the rest of the skeleton shows no changes. Carr⁸ described a diffuse osteosclerosis of the entire skeleton in one of his cases. Pende⁴¹ described changes on roentgen-ray of the sella turcica in all his cases and ascribed the disease to changes in the hypophysis and the region of the tuber infundibulum; most other writers have been unable to confirm these findings.

THE OPPOSITION

It would be far from accurate to state that the syndrome of metabolic craniopathy has met with undisputed acceptance. Schneider,⁵¹ in an article discussing the differential diagnosis of cranial osteoma and HFI, is skeptical of the clinical importance of the latter. In 1939 Tager and his associates⁵⁴ attempted to assess the clinical significance of HFI. Four hundred ninety-two patients seen consecutively over a two year period who complained of chronic difficulties were x-rayed. Sixty-six, or 13.4 per cent, showed diagnostic roentgen-ray changes; these included 20.7 per cent of the female patients and 1.1 per cent of the males. Twenty-six and two-tenths per cent of the cases occurred in females under the age of 15. Ten patients manifested neurologic syndromes, but the authors felt it impossible to assign the symptoms to the skull changes. Obesity and hirsutism did not figure prominently in their series, but in four cases these symptoms were present to the extent that they "were tempted to consider a pituitary factor." Carbohydrate

metabolism studied in 43 patients was normal. Calcium and phosphorus studies revealed no abnormalities. Hypogonadism was not present in a greater percentage than in the general population. The skull changes bore no relation to any particular body build. They concluded that the etiology and the possible clinical significance of the bony changes remain obscure.

Roth (1941) ⁴⁷ gave partial recognition to the syndrome. He described eight cases of Morgagni's syndrome studied at Bellevue Hospital. All were obese females; six had hirsutism. Four were frigid but there was no genital dystrophy. Hypertension was common. Seven cases showed abnormal glucose tolerance curves but only one had sugar in the urine. Creatinine was found in the urine of four patients, but the amount is not stated. One patient had hypercalcemia. Spinal fluid examination was normal except in the case of one patient who was suffering from a virus infection of the central nervous system. Clinical diagnoses of these patients included hypertensive encephalopathy (3), cerebral arteriosclerosis and bromide intoxication (1), epileptic deterioration, reactive depression, and delirious psychosis due to an infectious disease. Roth discounted the importance of the skull findings because their location could not account for the neurologic and mental changes. While admitting that the bony changes *can* produce psychic disturbances, he was convinced that many of these patients have no symptoms. (A possible answer to this argument has been discussed above.) Roth submitted his own theory of the pathogenesis of HFI, namely, "an increased permeability of the hematoencephalic barrier." This increase in permeability is the result of hypertension and arteriosclerosis. The flow of blood is slowed most along the points of greatest curvature where sedimentation of calcium takes place. Increased activity of the thyroid or hyperovarianism (pregnancy) can produce a similar train of events. Reading Roth's paper, one gains the impression he has made out a much better case for than against the existence of the syndrome.

In a carefully planned and well documented investigation, Schneeberg, Woolhandler and Levine ⁵⁰ evaluated the clinical significance of HFI seen at the Michael Reese Hospital. Of 150 clinic patients in whose cases for one reason or another skull films were indicated, the changes of HFI were found in four, an incidence of 2.7 per cent. Fifty hospital and clinic patients were rayed as controls. Six cases of HFI, or 12 per cent, were found. The authors therefore concluded that the presence of HFI was fortuitous and not related to concomitant symptomatology. They indicated that isolated case reports with the varied symptomatology noted in this paper were more or less invalid. They carried out statistical analyses of the individual symptoms and discovered that, with the sole exception of hirsutism, the alleged symptoms of HFI were less commonly found in their series of patients showing bony changes in the cranium than in those patients with normal skulls. So, for example, obesity occurred in 70 per cent of the controls and in only 31 per cent of those patients with skull changes; headache

in 54 per cent of the controls, compared with a figure of 29 per cent in patients with hyperostosis. Psychoneurotic complaints were equally common in both groups. Schneeberg and his colleagues emphasized that the severity of the symptomatology was not related to the degree or the progressiveness of the bony lesions; this has been admitted by proponents of the syndrome. The group at Michael Reese, in addition, described three cases with a syndrome similar to that of metabolic craniopathy without, however, the bony lesions. Both this and the preceding arguments have been answered by those who believe that the bony lesions are merely symptoms themselves of an underlying disorder and need not be present for a diagnosis to be made. Moore and others, as described above, have repeatedly stated that this is a constitutional disorder with certain pathognomonic bony changes which are exceedingly helpful in making the diagnosis but not essential. The bony changes, moreover, may require considerable time for their development and in the early stages they might be difficult to detect. Furthermore, while these changes are frequently slow in developing, they tend to be progressive, and the absence of symptoms accompanying the hyperostosis accidentally detected during routine examination is no guarantee that symptoms will not come into existence at a considerably later date. And finally, as stated above, in some cases the symptoms actually antedate the bony changes; these cases are probably more often missed than not. It is realized that these arguments no more prove the validity of the syndrome than those of the group at Michael Reese disprove it. What is sorely needed are *long term* observations on many patients with bony changes; a statistical breakdown of the clinical picture based on such data would be exceedingly important.

Henschen¹⁰ in his earlier work was not greatly impressed with the clinical significance of HFI (a view which he later considerably modified), but de Lehoczy and Orban⁹ believed that many of his cases were incomplete or abortive. They stated that metabolic craniopathy "is a syndrome, not a specific disease." Henschen¹⁰ found HFI in 50 per cent of females over the age of 50; he considered it to be associated with hormonal influences after the climacteric and not with pregnancy. At that time he believed it unnecessary and inaccurate to link the bony changes with the concurrent symptomatology into a definite syndrome; we shall see below how he modified this earlier view.

Eldredge and Holm¹² were impressed by the frequency of HFI in the group of insane patients reported by Sherwood Moore. They routinely x-rayed the skulls of 200 admissions to the St. Elizabeth's Hospital in Washington, D. C. Fifty patients, or 25 per cent, showed such bony changes, with a color incidence according to that expected from the general hospital population. They discounted the possibility of pressure by the enostoses being responsible for the symptoms because there were no neurologic symptoms that could be localized to areas affected by the proliferating bone. They

furthermore minimized the significance of the HFI because they noted that symptoms in patients without the bony changes frequently resembled those in patients with typical skull findings. There was no predominance of any particular mental disorder; dementia precox and the senescent arteriosclerotic conditions were the most common as one would expect. They believed that the cerebral atrophy found occasionally in the cases of HFI was entirely independent of the coexisting bony changes. These authors did not believe in the "triad of Morel" associated with HFI, "at least so far as the female population of a mental hospital is concerned." However, they admit hyperostosis to be present in female admissions to a mental hospital 20 times more frequently than in the general population, and they concede that HFI may be significant possibly as "a broad general factor in many mental disorders." They conclude by stating that they have no definitive answer to this problem, which still needs research. That statement is still appropriate today.

Schneeberg and his associates⁸⁰ review the evidence for the endocrine etiology of HFI and find it unacceptable; they list the large number of associated endocrine disorders found concurrently with the enostoses and consider the relation purely fortuitous. Moreover, they claim the great majority of patients with HFI evidence no endocrinopathies. They reject the applicability of Mortimer's production of cranial sclerosis in rats by the injection of "purified growth hormone" (v.i.) as proof of an endocrine etiology of the bony changes; they deny he produced true hyperostoses. They also deny that a sex-linked disease must necessarily have an endocrine basis, pointing to gout, male alopecia, and Buerger's disease as examples. They concede that they cannot explain the predilection of HFI for females. Not only was obesity not predominant in their series, but they also reject obesity as a metabolic disorder, pointing to the work of Newburgh on the exogenous character of *all* obesity. They further reject the implications of the term "metabolic craniopathy" by stating that they found no disorders of calcium or phosphorus metabolism in their patients; however, they admit that careful studies of calcium balance have not been carried out to date on reported cases. In conclusion, the authors state that their analysis of 675 cases from the literature (up to 1947) and 25 cases of their own indicates that "HFI is a not uncommon incidental skull thickening in women that is unrelated to whatever clinical state may accompany it." In at least one case in their series they believe harm was inflicted by leading the patient to believe she was afflicted with an incurable malady; this led to the fixation of her psychoneurotic tendencies, and the patient's obesity and headaches were not amenable to treatment as a consequence.

THEORIES OF PATHOGENESIS

Over the years a great many ingenious and interesting, if not very often plausible, hypotheses have been advanced to account for the formation of the

hyperostosis. It is well known that pregnancy may cause the deposition of bone on the inner table of the skull. Rokitsansky labeled these depositions "puerperal osteophytes," although he included in his reports a number of entities which do not properly fall into the group we are discussing; some of his original cases on review have been more correctly labeled inflammatory osteitis, tuberculosis, acromegaly, osteitis deformans, and so on. Moore³¹ cites Dreyfus as reporting hyperostotic cases in 30 per cent of his pregnant females. This phenomenon has also been labeled "physiological hyperpituitarism," or the "fugitive acromegaly of pregnancy." Henschen speaks of the "pregnancy syndrome," with softening of the skull, new bone formation, acromegaloid changes and pituitary acidophilism, although it must be pointed out that Henschen himself (who has been quoted by many writers, including Moniz, as attributing the changes of hyperostoses to pregnancy) denies this (1944). He believes the hyperostoses are due to postmenopausal changes, and feels that the changes occurring in pregnancy fall into a different category.

According to Moore's original thesis, therefore, HFI is a manifestation of a disorder of calcium and fat metabolism and "an expression of frustration in some phase of the function of reproduction." The menses, gestation and lactation, with their demands on calcium metabolism, suggested to him that in females there is a special structure for governing such metabolism. This mechanism does not cease its activity when the sexual life is over. As a result, the organism cannot release its excessive calcium, or, possibly, fat and calcium are absorbed beyond the capacity of the organism to metabolize them. Moore was unable to account for the localization of the calcium deposition in the calvarium, but in 1936, at any rate, he believed Morel's work implicated the third ventricle as the site of such a controlling mechanism. Ranson, Fischer and Ingram⁴³ stated that there is no nucleus in the hypothalamus whose complete integrity is necessary for the proper regulation of fat metabolism. Moore doubted the occurrence of this syndrome in the male (v.s). In this regard it must be pointed out, however, that only 50 per cent of the patients had borne children, many were single, and the syndromes described in connection with the bony changes do occur in the male.

Many of the more bizarre theories are reviewed in Beadles' article.⁵ Knies and Le Fever²⁴ in their review article give an interesting summary of many of the older theories. Cerebral congestion in mental patients as a cause of the formation of new bone has been suggested. Both Morel³⁵ and Grieg,¹⁶ separately, advanced the possibility that senile atrophy of the brain, especially of the frontal lobes, may play a rôle. The cerebral atrophy would result in negative intracranial pressure and this would exert traction on the dura, stimulating the new bone formation; this might also account for the frontal location of the enostoses. However, Henschen, who weighed the brains of individuals with and without hyperostosis, could find no significant

differences. It has also been suggested that the supine position of chronic mental patients, with the resultant localized congestion, favored new bone formation. However, the preponderantly lateral "fetal" position assumed by most senile patients would make it difficult to account for the symmetry of the lesions as they are usually seen; and the relative youth and activity of many subjects would tend further to invalidate this theory.

Grieg¹⁶ suggested hypercalcemia, with the "neutral" frontal bone taking up the "excess calcium." He also suggested that there might be in senile individuals absorption of calcium from areas of disuse and deposition in areas of use; this could occur in pregnancy and also in senility, where he postulated a saturation of the blood with calcium. Bertolotti and Nicotra speak of a chronic calcifying and ossifying pachymeningitis mediated by the lymphatics, possibly resulting from a chronic frontal sinusitis; this has rarely been found clinically. Moniz, who is quoted by Hemphill and Stengel,¹⁸ was led by his arteriographic studies to conclude that the symptoms were partially caused by increased intracranial pressure; other writers point out that osteoma rarely caused increased intracranial pressure and doubt that HFI is more frequently responsible. Trauma has occasionally been implicated; however, most writers agree that any effect exercised by trauma must be mediated via a derangement of the pituitary gland which secondarily causes the bony and the metabolic changes. Morel believed that contraction of the dura might cause the bony changes, but Moore indicated that the flat or sessile type of HFI would rule against such a mechanism.

Knies and Le Fever mention Henschen as the first to suggest an hereditary basis, but they claim to have reported the first such cases. However, as mentioned above, they overlooked the contemporary report of Hemphill and Stengel. There was a suggestive familial history in a number of the cases reported by Grollman and Rousseau.

Most of the more recent writers on the subject have implicated, directly or indirectly, the pituitary gland (and the hypothalamus) in the pathogenesis of the syndrome. Grollman believes metabolic craniopathy to be a distinct disease due to a hypothalamic disturbance. Moore,³³ in a personal communication, quotes Henschen as labeling HFI the "fifth pituitary syndrome." Certainly, the theoretical possibilities of such an association are tempting. Lichtwitz, discussing hypothalamic-pituitary syndromes, lists the following functions as dependent upon hypothalamic-pituitary activity: general metabolism, carbohydrate and fat metabolism, the distribution of fat, water metabolism (renal activity and sweating), thirst, hunger and appetite, growth and trophisms, sexual development, maturation and activity, cardiovascular activity (cardiac rhythm, blood pressure and vasomotor balance and circulating blood volume), gastrointestinal activity (secretions, tonus, peristalsis), formation of formed elements in the blood and plasma proteins, regulation of body temperature, sleep (hypothalamic only). In addition, the hypothalamus is essential for emotional expression which is normally restrained by cortical

control; in hypothalamic disorders, when cortical control is weakened, emotional instability and abnormal behavior come to the fore. Certainly this all-inconclusive list could adequately explain the symptomatology of HFI (and of most other diseases, too, for that matter). Even if one concurs with Schneeberg and his colleagues,⁵⁰ who believe that only the following clinical features are clearly of hypothalamic origin—diabetes insipidus, temperature and sleep regulation, disturbances, experimental obesity in animals, Froehlich's syndrome, experimental manic and rage-like syndromes, and possibly influences on the anterior pituitary causing precocious puberty, ovulation in rabbits, thyroid hypertrophy in response to cold (Selye's alarm reaction), and possibly hyperthyroidism—these, too, are varied and extensive enough to excite ready invocation of the pituitary and hypothalamic areas. The pituitary has been implicated by writer after writer, despite the very irregular appearance of definite pituitary and hypothalamic pathology in autopsied cases.

Mortimer^{37, 38, 39, 40} has carried out some interesting and pertinent experimental work bearing on the rôle of the pituitary in bony changes of the skull. In the Wistar strain of the white rat, hypophysectomy causes failure of the skull to continue growth and it remains at the stage of development during which surgery was carried out. In the adult rat there is hypoplasia of the calvarium, especially of the diploë; the frontal sinus or its homologue is hypoplastic, and there are characteristic tooth changes. Purified growth hormone extracted from the anterior pituitary restores the bones to normal. This is only temporary as anti-hormones are formed. Using crude alkaline growth extracts (containing the ketogenic factor), there is marked calvarial sclerosis and the animals become obese. These effects are only mild or entirely absent in the normal animal, but in hypophysectomized rats, as the animals become resistant to the ketogenic effect, the bony changes and the obesity become marked. Although, as has been pointed out above, Schneeberg and his colleagues criticized the comparison of this work with HFI, Mortimer himself states that "this is of special interest as affording a possible explanation for the high frequency of the association of cranial sclerosis and adiposity in women. . . ." Cranial sclerosis could also be produced by the prolonged administration of the parathyroid hormone.

On the clinical side, Mortimer, Levene and Rowe³⁹ reviewed the skull plates of 2,950 patients at the Evans Memorial Hospital. Four hundred ninety-four cases of "cranial dysplasia" were discovered, 63 per cent in females. It must be remembered that this was a rather select group, since most of them had undergone roentgen-ray examination of the skull as part of a workup for an endocrine dyscrasia, suspected or apparent. Sixty-five per cent of these patients had eventually proved to be endocrine disease cases, and 16 per cent of the roentgen-rays of the same series showed evidence of cranial dysplasia. On review of the histories, 57 per cent of the patients with films revealing dysplasias already had a pituitary diagnosis. If to these are

added the 14 per cent showing lesions of the central nervous system, and the 3 per cent female surgical castrates (both of these possibly affecting the pituitary, according to Mortimer, et al.), then 75 per cent of the clinical cranial dysplasias encountered in this series have a possible pituitary basis. Of the 494 cases, 12.7 per cent had previously and independently been found to suffer from a psychoneurotic or psychotic condition. Four types of dysplasia are described. Type I (274 cases). Acromegalic in type. The fifty-seven per cent of males in this group is in accord with the known clinical predilection of acromegaly for the male. Type II (130 cases). Earlier acromegalic type changes followed secondarily by sclerosis. The sclerotic changes are ascribed by the authors to *underfunctioning* of the pituitary gland. Only 10 per cent of this group were males. Combining types I and II, almost 82 per cent of the cases of cranial dysplasia are considered related to pituitary overfunctioning, whether sustained or not. Type III. All the cases were dwarfs, 10 of the 19 being males. There was failure of growth of the skull with lack of differentiation. Type IV contained 71 cases, only five of whom were males. The cranial size and proportions were similar to the skulls in type III but they were distinguished by well marked sclerosis of the calvarium, with some thickening of the skull. The majority of patients affected were obese and had significant menstrual disturbances, especially amenorrhea. In both types II and IV, the characteristics are sclerosis of the skull and obesity, and this combination occurs 10 times as frequently in female as in male patients. Type II, Mortimer believes, is the clinical equivalent of the injection experiments he carried out. He believed that both types give evidence of *hypopituitarism* with disturbances of carbohydrate and fat metabolism, with type II giving evidence of an earlier hyperfunctioning stage and type IV being consistently underactive.

Both Mellgren²⁸ and Henschen^{20, 21} consider Morgagni's syndrome (SM) a variant of the menopausal "Cushingoid habitus," especially since it occurs chiefly in postmenopausal females. Henschen found SM common in elderly females (11 per cent); if smaller enostoses were included, the percentage rose to 40. In females over the age of 70, he found the syndrome in 50 per cent of his case material. One-half of these showed the complete syndrome and only 12 per cent lacked both hirsutism and obesity. In reviewing the cases of 1,000 elderly females and 700 elderly males, he found 126 cases of SM and 93 "Cushingoid" cases (including a few cases of the genuine Cushing's disease). There were 143 cases of "defective" SM (lacking obesity or hirsutism); in this group there were 58 cases (21.8 per cent) of bony changes plus virilism, 35 cases of hyperostosis alone (12.2 per cent), and 50 cases of bony changes plus obesity (18.8 per cent). Unlike Mellgren, Henschen considers the syndrome absent, not merely defective, if the bony changes are not present. He also reported in the same series 189 cases of virilism (synonymous with marked hirsutism in his terminology), and 81 cases of marked obesity alone. Henschen believes that the neurologic and psychiatric

symptoms accompanying HFI must be considered "temporary or secondary connections." He sought clinical evidence of the endocrine nature of HFI; he found evidence of osteoporosis in 42.4 per cent of those with skull changes and in only 21.8 per cent of those without. Hypogenitalism was not infrequent, even in men with frontal enostoses. He stated that the weight of the heart in his female patients coming to post mortem was greater than warranted by the degree of obesity; this would point to hypertonia as a significant correlate. Diabetes is common in elderly obese individuals. Bartelheimer,^{3,4} as noted above, pointed out that the Cushingoid habitus and SM are very usual in diabetics refractory to insulin. (Houssay's and Long's experiments with anterior pituitary injections will be recalled at this point.) Henschen discovered diabetes quite frequently in SM, but there was no positive correlation between diabetes on the other hand and the *separate* symptoms of enostoses or hirsutism composing the SM. In general, there would appear to be a great deal more in common between SM and Cushing's disease than merely the external habitus. In both there is an increase of the corticotropic action of the anterior pituitary as measured by Jores' method. Bartelheimer and Cabeza (quoted by Mellgren)²⁸ noted an increase in this factor in 10 of 12 cases with the Cushingoid habitus, including incomplete cases, and in the only case of SM thus investigated. The corticotropic factor correlated with the diabetes and the obesity but not with hypertonia and diabetes. Jores also claimed an increase in this factor in 21 of 28 cases with hypertension. Henschen states that the menopausal connection of HFI is not shaken by the occurrence of enostoses in younger people, pregnancy, acromegaly and other endocrine pictures. He states that the process is different in the case of younger individuals particularly, although he gives no criteria for establishing the difference. It is readily noted that in his 1944 paper Henschen considerably modified his earlier opinion that Morgagni's syndrome had no clinical significance, was not connected with the coexistent symptomatology, and was simply a postmenopausal change (*not* associated with pregnancy, as quoted by others, including Moniz). At present, he believes that under certain circumstances HFI may have clinical significance and may be related to acromegaly and true Cushing's syndrome. His study of *clinical* material since 1936 forced him to the conclusion that certain cases are clinically significant. However, he criticizes the inclusion of cases without the bony changes as out of the bounds of the definition itself. He has also expressed some skepticism as to the admissibility of the broader conception of metabolic craniopathy as outlined by Sherwood Moore. He confined his careful analysis of his own material to the coincident presence of diabetes, hypertension, hypertensive heart disease, and neuropsychiatric symptoms, with the results outlined in the foregoing paragraphs.

Mellgren's work,²⁸ published in 1945 in Upsala, is an extensive research which has considerable significance in implicating the pituitary gland in Morgagni's syndrome. Mellgren was particularly interested in a quantitative

study of the special cell types appearing in the anterior pituitary in clinical conditions of enhanced function of the adrenal cortex. He included in these conditions, Cushing's syndrome, virilism and certain menopausal syndromes, viz. (a) the Cushingoid habitus, defined as hirsutism, usually only of the face, with obesity of the more or less "buffalo" type; and (b) the syndrome of Morgagni, which comprises the same clinical picture in combination with HFI.

As a result of a painstaking histologic study, including normal controls, Mellgren concluded that in both the menopausal syndromes and the adrenogenital syndrome the anterior pituitary gland is characterized by the degeneration of the basophils and an abnormal increase in the number of "special cells," although the changes are less marked quantitatively in the former group. The anterior pituitary gland showed similar changes in cases with and without the bony changes. Reider^{44,45} in his case found an increased number of hypertrophic amphophils and enlarged basophils. It is recognized that observers in the past had not been so successful in finding uniform pathologic changes in the pituitary. Morel, who examined the pituitaries of five of 17 old women with frontal enostoses, found a large chromophobe adenoma in one, predominance of the acidophils in three, scarcity of the basophils in two, and paucity of the chromophobes in two (note the overlapping). Henschen (1937) found an almost constant striking increase in both acidophils and basophils, accompanied by a decrease of the chromophobes. However, Mellgren claims that failure to employ the comparison microscopic technic vitiates these findings.

Mellgren concluded that the Cushingoid habitus and Morgagni's syndrome should be regarded as typical menopausal syndromes which bear a strong relationship to the adrenogenital diseases by virtue of morphologic and functional changes in the pituitary and adrenal glands. Whether this concept can be extended to metabolic craniopathy in general remains to be seen.

PATHOLOGY

Many of the salient features of the pathology have already been noted in the foregoing. The hyperostosis itself consists of eburnated cancellous bone with a densely adherent overlying dura. In Moore's second and third types there are condensation and occasionally thickening of the diploë. These changes are progressive. Occasionally in the frontal bone there is more marked evidence of osteoclastic activity than of osteoblastic changes. Beadles points out that senility, if it produces any changes at all, usually decreases the thickness and density of the skull.

As noted by Mellgren, despite the frequent clinical studies, anatomic studies of the endocrine glands have rarely been carried out. Each type of pituitary cell has been accused of being present in excess—or of being absent. Stewart,⁵³ who was the first to label the syndrome as one of "dyspituitarism,"

found "sclerosis" and deficiency of the chromophil elements. The hypothalamus has been implicated. In a later paper, Morel³⁶ retracted his statements concerning the significance of the changes in fat and pigment in the floor of the third ventricle. Henschen, too, had found such changes in control material of old women without enostosis. Two of the cases reported by Grollman and Rousseau did not show changes in the pituitary, thyroid or adrenals at post mortem.

Various changes have been found in the brain, and very frequently it is probable that these changes are not related to the HFI. Atrophy is common and this is nonspecific in type. In the case of Gerundo and Helwig,¹⁴ the brain was edematous and depressed bilaterally in front of Rolando's fissure and appeared molded by the hyperostosis. The frontal lobes were atrophic and the convolutions flattened by pressure. The parietal and occipital lobes were negative except for generalized edema. On gross examination, the sharp difference between the two areas suggested Pick's disease. The pituitary gland and the sella turcica were normal, as were the third ventricle and the basal ganglia. There was marked atrophy of the nerve cells in the frontal lobes and, here and there, glial proliferation. This is a typical report. Others have noted no significant changes in the brain. Pende⁴¹ described constant changes in the sella; these have not been confirmed by others.

Hemphill and Stengel,¹⁸ on examination of the pituitary gland, report only slight increase of the lymphocytes and small degree of proliferation of the connective tissue, but insufficient to justify the term "sclerosis." They emphasize that one must be guarded in his conclusions in describing changes in the pituitary gland, pointing out the great variations of the normal seen, especially microscopically. For example, lymphocytic infiltration is seen in a high percentage of pituitary glands in individuals dying with chronic infections. They interpreted an unusual increase in the oxyphil cells in three small parathyroid glands, and the presence of a fourth entirely composed of oxyphil cells with signs of degeneration, as indicating abnormal parathyroid function. Although the percentage of oxyphils increases with age, especially in females, the authors believe a gland composed entirely of oxyphils is abnormal. They postulate that a low grade parathyroid hyperfunction over a long period might produce sclerotic changes without the cystic formations characteristic of marked overactivity, and might account for the long periods during which the blood calcium studied clinically might appear normal. Whether this activity is primary or secondary to a parathyrotropic hormone is left in doubt. In their cases there was moderate atrophy of the thyroid and adenomatous hypertrophy of the adrenals, the latter being the result of stimulation by the pituitary and probably the cause of the virilism.

DIFFERENTIAL DIAGNOSIS

There is usually not much difficulty in distinguishing the bony changes from other diseases of the skull. The salient feature is the limitation of the

bony changes to the inner table and the diploë, without any changes in the external contours of the skull. Thus one can immediately differentiate such conditions as rickets, congenital lues, external osteomas, acromegaly, Paget's disease, and leontiasis ossea by simple inspection. The bony changes accompanying blood dyscrasias or disturbances of calcium metabolism may be ruled out by characteristic accompanying symptoms. Osteosarcoma is ruled out by its characteristic roentgen appearance and rapid progressiveness. Osteomyelitis also produces destructive changes of a more rapidly advancing nature. Dural endothelioma is usually unilateral and more localized than HFI. The compensatory bony overgrowth sometimes seen in senility is generalized and not limited to the internal table. Localized luetic or tuberculous osteitis may provide difficulties, but osteoclastic activity can usually be detected. Moore recommends stereoscopic roentgen-rays, bilateral and posteroanterior, and examination of the optic foramina taken routinely.

More difficult is the diagnosis on clinical grounds. As has been seen from the foregoing, almost any neurologic or psychiatric disorder may enter into the differential diagnosis, and it would be futile to list these. Moore states that if the diagnosis is suspected, one should meticulously seek a history of cranial nerve involvement, disturbance of calcium, phosphorus and acid-base metabolism, and carry out encephalography in an attempt to explain the mental symptoms.

Acromegaly often enters into the differential diagnosis since many of these patients, including our own, present "acromegaloid" features. Cushing's disease must be ruled out in some cases; Grollman¹⁷ claims that metabolic craniopathy lacks the purplish striae, acrocyanosis, "osteopetrosis," and rapid progressiveness of Cushing's disease. In addition, there is not true masculinization in HFI, such as enlargement of the clitoris, voice changes, and so on. Determination of the 17-ketosteroids is valuable; in all of Grollman's cases, the values were normal.

PROGNOSIS

Moore states that "the psychic manifestations if progressive terminate in dementia; if less fully developed, the patients appear doomed to chronic invalidism." Knies and Le Fever,²⁴ in a similar vein, note that "the average case of metabolic craniopathy has as its future only the status quo, or gradual progression, considering our present time diagnosis and modes of treatment." Whereas Knies and Le Fever comment that remarkable improvement and variability may at times occur, as in two of their cases, one gets a very vivid impression from reviewing the literature that this syndrome is the cause of serious morbidity and loss of productivity in those unfortunate individuals afflicted with it. It must occasionally be considered as a cause of mental retardation in youngsters. In general, the morbidity may extend over many years, occasionally half to three-quarters of a lifetime.

TREATMENT

As might be expected from the gloomy prognosis outlined above, therapy has not been dramatically successful. Aminoacetic acid (Moore recommends 10 gm. of gelatin three times daily over a long period of time) and chondroitin have been reported occasionally as giving favorable results, especially in relieving the headache and the muscular weakness. Two of Knies and Le Fever's patients showed dramatic improvement on 40 to 60 grains of chondroitin daily. Vitamin B₁ has been recommended for weakness. Luminal has been used to counteract the spasticity and the exaggerated tendon reflexes. Moore in his original papers recommended a rachitogenic diet and parathormone. Anti-luetic therapy has been of no avail except in an occasional case, and it is likely in such cases that the diagnosis was inaccurate. Because of the frequent low level of the basal metabolic rate, thyroid has been used, usually with poor results. Ergotamine tartrate and posterior pituitary extract have been used with indifferent results in the treatment of the cephalalgia. Bartelheimer used progynon in the treatment of headache, with moderately successful results. Knies and Le Fever suggested irradiation of the pituitary-hypothalamic area because of the similarity of the headaches to those complained of by menopausal patients. Grollman found these treatments rarely afforded striking results. Other writers, admitting occasional gratifying results, are reluctant to irradiate these areas as a routine. Radiation of the frontal bone itself has been tried (Pende). In a personal communication, Moore writes that Glen Spurling has had success in relieving the headache by ligation of the middle meningeal artery; in this case, however, an occipital headache remained and, moreover, as Moore admits, this is a rather extensive piece of surgery. Many of the authors suggest decompression by bone flap for headache and for other major symptoms, such as Jacksonian epilepsy, choked optic discs, and so on. However, these "focal signs" are usually lacking and, moreover, this suggestion has an academic note, for nowhere in the literature can one find mention that such a procedure actually has been carried out deliberately, although there is a strong possibility that such operations may have been performed under the erroneous impression that a cerebral neoplasm existed. Unquestionably, the close attachment of the dura to the enostoses would make such a procedure extremely hazardous. More important, it has been demonstrated that in most cases the bony changes themselves are not the source of the patient's complaints but merely another one of the concurrent findings.

Fever therapy, tried in one case by Knies and Le Fever, was ineffectual. Grollman recommends that these patients be treated for their obesity by the usual methods. Many of the patients have been given orthodox psychotherapy.

Hopes for a more rational—and more successful—therapy must rest on future clinical and laboratory investigation which will unravel the endocrine puzzle presented by this syndrome.

CASE REPORT

The patient was first admitted on May 30, 1946. She was 28 years old at the time, and complained that she had developed severe occipital headaches and marked polyuria and polydipsia on April 6, 1946. This had followed a severe emotional shock upon learning that her husband had lost a highly desirable job. The patient stated she was urinating every 15 to 20 minutes, day and night. There were no fever or chills, blurring, diplopia or other disturbance of vision, and no vomiting. The symptoms had continued unabated since the onset. There was severe dryness of the mouth. There was no history of trauma, infection, venereal disease, or use of any medications. The urine was pale and there had been no evidence of blood. There was no dysuria. The patient had noted a moderate gain in weight (10 lbs.) during the past several months, without showing evidence of peripheral edema.

The past history included the usual childhood diseases. The patient had always been in good health. The only possibly significant finding was that of an attack of giant urticaria in November, 1945, again following an emotional upset. The onset of the menses was at 13 years of age, with periods occurring every 28 days and lasting five days. The last menstrual period was on May 16, 1948, and this period had lasted only three days. She had severe dysmenorrhea. Para III, Grava III. All three children are alive and well.

Physical Examination: Temperature, 99.4; pulse, 92; respirations, 20. The patient was a well developed, slightly obese young white female who appeared apprehensive but not ill or in any distress. She complained of severe head pain and seemed to have some degree of photophobia. The patient was alert and well oriented. Intelligence was good; excellent contact was made with the examining physicians. The patient could have been described as handsome; however, there was a masculine cast of the facies, and some observers suspected acromegaly in a very early stage at the original examinations. There was no hirsutism. The head showed no gross abnormalities. The pupils were round, regular and equal. They reacted to light and accommodation. The movements of the extraocular muscles were normal. The discs were well developed and of normal color. The fundal blood vessels showed no changes. The teeth were in good condition. The vision of the right eye was 20/30, left eye, 20/20. The papillae of the tongue were well developed. The mucous membranes of the mouth and pharynx were negative. The neck was supple, and no masses, tracheal deviation, or engorged vessels were noted. *Chest:* Breasts were moderately obese; no masses or tenderness. The lungs were clear to percussion and auscultation. The heart was not enlarged. The PMI was in the fifth intercostal space inside the midclavicular line and there were no thrills or murmurs. The rhythm was regular. A_2 was louder than P_2 . The blood pressure was 120/80. *Abdomen:* Soft and moderately obese. There were no palpable masses or viscera. There was no tenderness. There were no enlarged lymph nodes present. The skin was clear and there was a normal female distribution of the hair. Rectal examination was negative. Pelvic examination revealed no abnormalities. The cervix pointed posteriorly. The uterus was not enlarged. There was a slight amount of mucoid vaginal discharge.

Neurologic Examination: The cranial nerves were intact. There was no loss of any of the modalities of sensation. There was no loss of motor power. The deep tendon reflexes were active and equal. There were no abnormal reflexes present.

The original impression was that this was a genuine case of diabetes insipidus. Some observers felt that hysteria should be ruled out.

Laboratory Data: Blood: Hemoglobin, 90 per cent; red blood cells, 5.0 M.; white cells, 20,000, with 50 per cent polys and 50 per cent lymphocytes. Blood chemistries: sugar, 112.3 mg. per cent; urea nitrogen, 8 to 14 mg. per cent; uric acid, 2.6 mg. per cent; chlorides, 440 to 460 mg. per cent.

Blood Kline test was negative. Spinal fluid examination on June 6 showed normal pressure, 83.3 mg. per cent of sugar. The spinal Wassermann test was negative. Colloidal gold, 1111000000. Blood cholesterol, 217 mg. per cent, with 65 per cent esterification. Numerous urine examinations were negative for sugar, albumin and formed elements. Specific gravities ranged between 1.000 and 1.014, usually varying between 1.003 and 1.006. Basal metabolism was -2 . Glucose tolerance test showed fasting blood sugar of 80 mg. per cent, with successive half hourly specimens at 155, 130, and 90 mg. per cent, respectively.

Roentgen-ray examination of the chest showed normal heart and lungs. There was no evidence of demineralization of the bones of the skull or the hands. In the skull, however, there was reported evidence of osteitis frontalis interna, with a slightly increased prominence of the digital markings in the posterior half of the skull.

Course in Hospital: The patient continued to complain of severe occipital and frontal headaches, insomnia, and frequency of urination. Sample daily intake on June 4 was 8,150 c.c., with a urinary output of 9,625 c.c. The patient seemed more upset, however, by the headaches than by the polyuria. She was placed on gradually increased doses of surgical pituitrin, but was not satisfactorily controlled until she was receiving a total of 5 c.c. of pituitrin daily, with distribution as follows: 2 c.c. at 7:00 a.m.; 1 c.c. at 2:00 p.m., and 2 c.c. at 8:00 p.m. However, it was noted that even on this regime the patient could not be regularly controlled, and the urine output on 5 c.c. of pituitrin daily varied from 1,500 to 5,600 c.c. over 24 hour periods. It was difficult to determine whether emotional upsets precipitated the periods of polyuria or were caused by them. On the whole, however, she was fairly well controlled by this dosage while in the hospital. She complained of indurated areas of the buttocks and arms where the injections were administered. Because of this, an attempt was made to use pituitrin nasal jelly to avoid the frequent injections. This had to be discontinued, however, because of the patient's inability to cooperate in this procedure. She was put back on pituitrin extract, 5 c.c. daily.

A neurologic consultant saw the patient on June 6 and noted the following: (1) Obesity. (2) Definite hyperextensibility of all the joints. (3) Peculiar doughy feeling on pressure of the skin, suggestive of myxedematous changes. This was generally distributed. (4) The body contour was similarly suggestive of myxedematous changes. (5) There was a definite but moderate nystagmus of the left and right lateral gaze. (6) Neurologic examination otherwise negative. He pointed out that the headache was of an interesting type, generally confined to the right side of the head, worse in the morning and evening, and associated with concomitant tearing of the right eye. He felt that the patient had disease of the hypothalamic area because of the headache and associated lacrimation and the other evidence of metabolic disturbances.

By June 10, the polyuria had been fairly well controlled and at this time the headaches became the predominating symptom. The patient was obviously in severe distress and would cry out with pain. She did not respond to caffeine, aspirin, codeine, and the other usual analgesics. Treatment of the polyuria was interrupted from time to time by the fact that the hospital supply room ran out of pituitrin. This necessitated contact with the manufacturer on several occasions. On June 19, in order to rule out hysteria, the patient was given distilled water by hypodermic instead of the usual dose of pituitrin, following which the urinary output rose to 6,500 c.c. She expressed great dismay and apprehension that the "drug" was no longer effectual. The usual doses of pituitrin were restored and the polyuria ceased. She was discharged on July 1 on a maintenance dose of 5 c.c. daily, with relief of her polyuria and slight improvement of her headaches. The patient visited many private physicians following her discharge but made no further improvement. Because of the fact that three injections daily were causing increased induration of her thighs and buttocks and arms, making

further injections difficult, she returned to the hospital on July 30, 1946, for recalibration with pitressin tannate in oil.

On this admission, no changes in the physical findings were noted except for the presence of nodules at the sites of the pituitrin injections. It was felt that in part, at least, the irregularity of response to the pituitrin might be due to the injection of potent substance into scar tissue, a disturbing factor that occasionally interferes with the control of diabetics.

Laboratory Data: Repetition of all the tests above showed no changes. The white cells numbered 8,400, with 48 polys, 48 lymphocytes and 4 monocytes. The sedimentation rate was normal. Blood calcium, 9.5 mg. per cent, and phosphorus, 2.8 mg. per cent. Tangential roentgen-rays of the skull in the region of the right parietal and frontal bones showed generalized thickening of the inner table of the calvarium, "suggestive of metabolic craniopathy." Roentgen-rays of the cervical spine were normal.

Course in Hospital: It was found that 4 to 5 c.c. (20 to 25 pressor units) of pitressin tannate in oil satisfactorily controlled the polyuria for 72 hours. It was noted that, since the onset of her illness in April, the patient was having short menstrual periods with scanty bleeding. Also, it was noted that there was some loss of hair in the right frontotemporal region, with marked hyperesthesia over a diamond-shaped area measuring about 6 cm. along each side. It was believed the loss of hair was due to the patient's constant rubbing in a futile effort to ease the pain. Neurologic consultant during this admission suggested the possibility of a temporal arteritis with an associated sympathetic disorder around the temporal artery to account for the lacrimation. He did not believe there was any indication for neurosurgery. Dental examination revealed normal teeth. In an attempt to relieve the headache, the diamond-shaped area referred to above was infiltrated with 1 per cent procaine down to the periosteal layer. This had the effect of aggravating the headache. A second injection in this area was also unsuccessful. The patient was discharged on August 15, 1946, on a maintenance dose of 4 c.c. of pitressin tannate in oil. From that time she had an irregular course insofar as the polyuria was concerned. The maintenance dose would suffice for variable periods, ranging from 18 hours to three days, without any obvious reason for the fluctuation, either physical or emotional, aside from the possibility of injection into indurated or scarred areas noted above. The patient was studied at two university hospitals in this city without additional findings or therapy. The oligomenorrhea continued. She was greatly disturbed by her headaches, and stated that the polyuria was a relatively mild annoyance by comparison. She became despondent and threatened suicide. At this time it was first suspected that all her complaints might well fit into the syndrome of metabolic craniopathy, and the case report and original roentgenograms were sent to Dr. Sherwood Moore, who was kind enough to review them and confirm the diagnosis.²⁸ He classified the roentgen-ray changes as being of the diffuse type. He described one of his cases where ligation of the middle meningeal artery had been carried out for the relief of head pain, but admitted that an occipital component of the pain still persisted, and he did not recommend this procedure with enthusiasm. He recommended the use of glycine, and the patient was instructed to take a tablespoonful four times daily. She took this for about two weeks and then discontinued taking the drug because "it had not helped," this despite the fact that she had been forewarned a long trial period was necessary. Also following Dr. Moore's suggestions, she was sent to a mental hygiene clinic for psychotherapy, but after a few sessions she ceased attendance, again stating she had not been helped.

The patient had a fixed idea that pregnancy might ameliorate her condition, and she had been trying for some time to conceive. She ceased menstruating August 25,

1947. Until January 14, 1948, the pregnancy was uneventful except for occasional abdominal cramps following the administration of pitressin tannate. On that date she reported a slight spotting. This continued for about four days; the uterus at that time was reported the size of a three and one-half months' gestation. There was no further increase in the size of the uterus; the Ascheim-Zondek test on March 8 was negative, and roentgen-rays showed no fetal parts. For a while, the possibility of pseudocyesis in an emotionally labile female was entertained. However, on April 17, 1948, she developed abdominal pain and vaginal bleeding, and the diagnosis of missed abortion was made. The uterus at this time was still the size of a three months' pregnancy. The uterus was emptied with sponge sticks of a macerated fetus.

During pregnancy, the patient stated that a dose of pitressin tannate in oil was effective in controlling the polyuria for intervals of from three to seven days; since the abortion, she has needed daily injections. Headaches are uncommon at present and are brought on by excitement. The scalp is still tender to the touch. She complains bitterly at present of thirst, polyuria, weakness, and dizziness. Her weight has increased from 165, when first seen just a little over two years ago, to 183; there was no undue increase during pregnancy. This was predicted by Dr. Moore. There has been no development of hirsutism. Menses are now regular. The patient tried insufflation with the powdered preparation of the posterior pituitary but it made her nauseated and she discontinued it. She now relies on the intramuscular injections of the oily preparation. She has a slight acne, and her features are somewhat coarser and more masculine than when she was first seen; the acromegaloid appearance is more striking. Roentgen-rays taken in June, 1948, show no progression of the bony changes. She remains an intelligent, relatively cooperative individual (despite her discontinuing certain therapeutic measures) who, aside from some "nervousness" and natural anxiety about her condition, is well oriented and in good contact with her environment. Her complaints have not prevented her from carrying out her duties as a housewife in a satisfactory manner.

DISCUSSION

We believe this case has a unique interest because of the presence of diabetes insipidus accompanying the other features of metabolic craniopathy. There has been some objection to the diagnosis of diabetes insipidus because of the occasional relatively high specific gravity of the urine; however, most of the time the specific gravity has varied between 1.000 and 1.006, and we do not believe that occasional elevation mitigates too strongly against the diagnosis. The psychiatric consultant felt this was not an hysterical phenomenon, and the clinical course and response to therapy have been those of a true diabetes insipidus.

Cases of diabetes insipidus complicating metabolic craniopathy are rare; with the sole exception of Maranon's case (v.i.),²⁶ I have been unable, in reviewing most of the literature, to find another case that compares with this. Although most writers on the subject dutifully list diabetes insipidus as a possible symptom in the complex of HFI, case reports are notably lacking. In many cases the polyuria was apparently mild and could be accounted for by the diabetes mellitus that coexisted. Moore³⁸ states that patients with HFI "frequently do have urinary findings such as polyuria, polydipsia, etc., but not necessarily a true diabetes insipidus." He does not amplify on the

differentiation. Certainly, in our case, one would find it quite difficult to detect clinical or laboratory differences from a case of diabetes insipidus unaccompanied by HFI. The presence of diabetes insipidus as a symptom in this complex tends further to implicate the pituitary-hypothalamic region in the genesis of HFI. Lichtwitz²⁵ states that diabetes insipidus is the result of a disorder of the anterior hypothalamus, and is controllable by the pituitary antidiuretic hormone which is found and probably produced not only in the posterior lobe but also in the tuberal region. Therefore, total hypophysectomy need not eradicate the source of the hormone and does not necessarily produce diabetes insipidus. However, failure to respond to the hormone may exist and diabetes insipidus may result in spite of the presence of a normal pituitary gland. On the other hand, both Mann and Jones²³ believe that diabetes insipidus cannot be produced in the absence of the anterior pituitary which produces a diuretic hormone. Lichtwitz denies this. However, Jones states that the anterior pituitary acts in the following ways: (1) maintains general metabolism, including water exchange; (2) secretes the thyrotropic factor which in turn, by its action on the thyroid gland, increases general metabolism and water exchange; (3) secretes a specific diuretic principle which acts in conjunction with the thyroid hormone; and (4) possibly produces diuresis by stimulating the secretion of the adrenal cortex. In connection with the last, experimentally, a diabetes insipidus-like state has been produced with injections of desoxycorticosterone acetate.

Lichtwitz points out that thirst may be a hypothalamic symptom: here the administration of posterior pituitary extract will cause water intoxication. This was not the case with our patient, another reason why we believe the diagnosis to be sound. It is generally believed that the polyuria precedes and causes the polydipsia, although Bellows and Van Wangenen (quoted by Lichtwitz) have produced some good experimental evidence pointing to the opposite view.

Therapy suggested in the past has included aminopyrine, especially combined with sedatives and atropine, fever therapy, follicular hormone (because of its depressant effect on the anterior pituitary and the hypothalamus), antithyroid drugs or thyroidectomy to nullify the diuresis-enhancing effect of the thyroid gland, antiluetic therapy in specific cases, spinal drainage where there is increased intracranial pressure, and, of course, the various preparations of posterior pituitary substance. In our case, pitressin tannate in oil has proved to be the most satisfactory medication; the watery preparation required frequent injections and the patient was unable to tolerate the powdered or jellied nasal preparations. Blumgart, who introduced the powder, admitted that some patients develop nasal catarrh.

Spontaneous amelioration of the diabetes insipidus state is a familiar phenomenon. Our patient has not been particularly troubled by disturbances due to nocturia, nor was the patient reported by Maranon,²⁶ this despite the edict by some clinicians of "no nocturia, no diabetes insipidus." Diabetes

insipidus may last through life and is not incompatible with long life. It is frequently milder after the age of 50. Rest is helpful. Pregnancy may relieve or exacerbate the complaints; in our case, there is some suggestive evidence that the symptoms have grown slightly more severe.

Maranon reports an interesting case of uterine atony in a patient with diabetes insipidus. This patient, whom he had observed over a period of 26 years, had two pregnancies, both marked by extreme atony of the uterus. During the second pregnancy labor could be maintained only by the periodic administration of posterior pituitary extract; parturition was successfully concluded in this manner. The uterine atony and missed abortion of our case will be recalled; the obstetric implications of this case will be reported elsewhere. There are several interesting features in Maranon's article. He believes diabetes insipidus is entirely functional, and disagrees with Duncan's classification¹⁰ into essential and symptomatic types. His patient's symptoms began following an immersion (and fright!) at the age of 17. On several occasions she has had severe attacks of headache, some with vomiting, scintillating scotomas, and spasticity and paresthesiae localized to the limbs of the left side. He believes that these symptoms (usually following an injection of pituitrin), plus the spontaneous unilateral hypertrophy of a breast, might point to a small midbrain lesion which has existed for many years. However, he adds that the patient's skull films show "slight frontal hyperostosis," and we are suggesting that this case may be one of metabolic craniopathy and closely linked with ours.

Where diabetes insipidus is not a complication, HFI appears to offer no special difficulties in pregnancy. Ruch⁴⁸ reports a case of a 31 year old white female who during her first pregnancy had gained 70 pounds and developed severe headaches. HFI was found. Following delivery, these symptoms gradually disappeared except for recurrent headaches. She was seen by Ruch during the fourth month of her third pregnancy, suffering from severe headaches. There was hirsutism of the face, abdomen and thighs, and suggestively acromegalic features. Termination of the pregnancy was not considered indicated. In general, a review of the literature does not give any impression of a trend of the symptoms during pregnancy for better or worse.

CONCLUSIONS

1. A review of the literature gives one the impression that the syndrome of metabolic craniopathy exists as a clinical entity. While it is admitted that frequently the clinical picture has been poorly defined, and while undoubtedly certain of the patient's complaints in individual case reports have been linked unjustifiably with the bony changes on the grounds of mere coincidence, throughout the case material reviewed certain symptoms appear to be almost ubiquitous and certainly present in far higher percentages than one would expect from the statistics of chance. Such symptoms include obesity, head-

ache, and hirsutism. The headache particularly, because of its rather characteristic tenacity, distribution, and associated scalp tenderness, is an especially valuable clinical criterion in establishing the diagnosis. Other symptoms, such as hypertension and muscular weakness, would appear to be of secondary importance in establishing the diagnosis, adding to the strength of the diagnosis when the more characteristic signs and symptoms are present in addition. The rôle of the neurologic and psychiatric symptoms is exceedingly difficult to assess; these are admittedly highly nonspecific, and more study of their significance is indicated. Both the proponents and the opponents of this syndrome have been guilty of errors in logic in assessing the validity of the syndrome, the former by cheerfully accepting a host of complaints in causal relationship to the bony changes, and the latter by pointing to the absence of the same complaints in patients with typical bony changes. At least one approach to the problem must be the long term study of patients with asymptomatic HFI. The statistical approach of Schneeberg and his associates was a good start in this direction (and virtually the only paper of its type, at least to my knowledge), but here, too, the absence of long term followups vitiated some of the conclusions. Unquestionably, a certain percentage of patients manifesting the bony changes will remain asymptomatic throughout life; unfortunately, we have no reliable statistics as to this group. But the existence of these incomplete or abortive forms can hardly be raised as vital evidence against the frequent clinical significance of the bony changes; practically every recognized endocrinologic syndrome has its quota of *formes frustes*. As the situation stands at present, it would appear that the syndrome of metabolic craniopathy is genuine, and the problem is not one of dismissing it summarily but rather one of carefully defining and limiting its clinical features, so that the alert clinician may be led to consider this syndrome in a differential diagnosis before roentgen-rays focus his attention on the bony changes and even (as emphasized by Knies and Le Fever and Grollman and Rousseau) in the absence of roentgen-ray changes.

2. The experimental work of Mortimer and of Mellgren provides some substantial basis for the clinical impression that the pituitary-hypothalamic region is involved in the genesis of the syndrome. While objections can be raised to the applicability of Mortimer's experiments on rats to human beings, and while Mellgren's work requires confirmation and was limited to Morgagni's syndrome only, their work would tend to support Henschen's statement³³ that the clinical picture associated with the bony changes of the skull is indeed "the fifth pituitary disease." It is possible that new technics, particularly in the field of hormone assay and histologic study, will be of help in delineating more clearly the endocrine status of these patients in the future.

3. In conclusion, one should think of metabolic craniopathy when a middle aged or elderly female complains of obesity, persistent cephalalgia,

and hirsutism. If in addition she is hypertensive and complains of muscular weakness and menstrual disturbances, the clinical impression is strengthened. If, further, there are a variety of mental and neurologic disturbances pointing in general to interference with the higher mental functions and focal disease of the cranial nerves in the absence of a specific etiologic agent, these may be considered as secondary supporting features. The presence of roentgen-ray changes of the skull is a comforting but not essential finding. It is obvious that, in the absence of the more common symptoms, the relationship of rarer complications, such as diabetes insipidus, etc., to the bony changes would be more difficult to evaluate.

4. Treatment at present is unsatisfactory. Glycine in large doses should be tried, and possibly irradiation therapy should be attempted more frequently. The status of treatment will depend on a more definite understanding of the pathogenesis of the syndrome.

SUMMARY

1. A review of the literature of metabolic craniopathy is presented. While the frequently vague and indefinite nature of the complaints is admitted, there is much suggestive clinical and experimental evidence pointing to this syndrome as a clinical entity, probably endocrine and possibly pituitary in origin.

2. A case of metabolic craniopathy, complicated by diabetes insipidus and uterine atony during pregnancy, is described.

3. The clinical implications of this syndrome are very broad. Much more clinical and laboratory investigation needs to be done before this syndrome can be placed on a firm basis, diagnostically and therapeutically.

Appreciation is expressed to Dr. J. J. Guttman for advice on the preparation of this paper.

ADDENDUM

CASE HISTORY

The patient became pregnant in June 1948. During this pregnancy she abstained from the use of pitressin and as a result the polydipsia and polyuria were very severe. In February she was admitted for mild toxemia; her weight had gone rather suddenly from 186 to 206 pounds, there was some vomiting and her blood pressure rose to 150/100 (on one occasion only). The blood chemistry studies were normal. The fundi were normal. She was treated with salt restriction with some improvement. She was delivered of a normal male infant on March 31, 1949.

Her status has remained fairly constant since that time. The headaches are milder in character and she does not complain as much as in the past. She takes pitressin irregularly and as a result is forced to urinate every 20 to 30 minutes and rises during the night every hour or two. Recently she has received "adjustments" from a chiropractor and states she is improved; however, the improvement consists of a subjective sense of well-being; the polyuria continues as previously. Her weight has increased by 44 pounds since she was first seen. Roentgen-rays of the skull taken during the last pregnancy did not show progressive changes.

We have followed this patient for four and one-half years at the present time. This represents the longest single followup period of a case of metabolic craniopathy described in the literature.

BIBLIOGRAPHY

1. Andrews, C. T.: Hyperostosis frontalis interna, *Brit. M. J.* **2**: 185-187, 1942.
2. The hypothalamus and central levels of autonomic function, *Assoc. Res. Nerv. and Ment. Dis. Research Publications*, Vol. 20, 1940, Williams & Wilkins Co., Baltimore, p. 416-435 (Kendrick Hare—Water Metabolism: Neurogenic Factors); p. 436-438 (I. Gersh—Water Metabolism-Endocrine Factors).
3. Bartelheimer, H.: Hyperostosis frontalis interna und hypophysärer Diabetes, *Wien. med. Wchnschr.* **89**: 341-343, 1939.
4. Bartelheimer, H.: Die Hyperostosis frontalis interna als Symptom der hypophysären Diabetes, *Deutsche med. Wchnschr.* **65**: 1129-1130, 1939.
5. Beadles, C. F.: The cranium of the insane, *Edinburgh M. J.* **5**: 263, 388, 501, 1898.
6. Brauns, W. H.: Hyperostosis frontalis interna, *Bull. New England M. Center* **6**: 267-276, 1944.
7. Canavan, M.: Enostoses of the calvarium, *Arch. Neurol. and Psychiat.* **39**: 41-53, 1938.
8. Carr, A. D.: Neuropsychiatric syndromes associated with hyperostosis frontalis interna, *Arch. Neurol. and Psychiat.* **35**: 982-989, 1936.
9. de Lehoczy, T., and Orban, A.: Hyperostosis frontalis interna (Stewart-Morel syndrome), *Brit. M. J.* **1**: 1049-1050, 1938.
10. Duncan, G. (editor): *Diseases of metabolism*, Ed. 2, 1947, W. B. Saunders Co., Philadelphia.
11. Eisen, D.: The internal frontal hyperostosis syndrome, *Canad. M. A. J.* **35**: 24-27, 1936.
12. Eldredge, W. W., and Holm, G. A.: Incidence of hyperostosis frontalis interna in female patients admitted to a mental hospital, *Am. J. Roentgenol.* **43**: 356-359, 1940.
13. Feiring, W.: Coexistence of gout and metabolic craniopathy, *New York State J. Med.* **46**: 631-634, 1946.
14. Gerundo, M., and Helwig, G. F.: Morgagni's syndrome—hyperostosis frontalis interna, *M. Rec.* **156**: 31-33, 1943.
15. Gilbert, J. P.: Stewart-Morel syndrome or syndrome of internal frontal hyperostosis, *J. Tennessee M. A.* **35**: 176-178, 1942.
16. Grieg, D. M.: On intracranial osteophytes, *Edinburgh M. J.* **35**: 165, 237, 1928.
17. Grollman, A., and Rousseau, J. P.: Metabolic craniopathy, *J. A. M. A.* **126**: 213-217, 1944.
18. Hemphill, R. E., and Stengel, E.: Morgagni's syndrome: a clinical and pathological study, *J. Ment. Sc.* **86**: 341-365, 1940.
19. Henschen, F.: Hyperostosis verrucosa frontalis interna und deren Bedeutung, *Acta path. et microbiol. Scandinav.* **13**: 95-97, Suppl. 26, 1936.
20. Henschen, F.: Über die verschiedenen Formen von Hyperostosis des Schädeldachs, *Acta path. et microbiol. Scandinav.* **15**: 236-246, Suppl. 37, 1938.
21. Henschen, F.: Über die klinische Bedeutung von Morgagni's Syndrom, *Acta path. et microbiol. Scandinav.* **54**: 617-642, 1944.
22. James, T. G. I.: Hyperostosis frontalis interna, *Brit. J. Radiol.* **9**: 750-752, 1936.
23. Jones, G. M.: Clinical observations on the etiology of diabetes insipidus, *Texas State J. Med.* **40**: 583-585, 1945.
24. Knies, P. T., and Le Fever, H. E.: Metabolic craniopathy, *Ann. Int. Med.* **14**: 1858-1892, 1941.
25. Lichtwitz, L.: Hypothalamic pituitary syndromes, *Bull. New York Acad. Med.* **15**: 773-789, 1939.
26. Maranon, G.: Diabetes insipidus and uterine atony, *Brit. M. J.* **2**: 769-771, 1947.
27. McGavack, T. H., and Reinstein, H.: Brachydactyly, polyphalangism, and brachymetapodism in a moronic individual with microcephaly, internal frontal hyperostosis and endogenous obesity, *Am. J. Roentgenol.* **45**: 55-62, 1941.
28. Mellgren, J.: The anterior pituitary in hyperfunction of the adrenal cortex, *Acta path. et microbiol. Scandinav. Suppl.* **60**, pp. 1-177, 1945.

29. Moore, M. T.: The Morgagni-Stewart-Morel syndrome, *Arch. Int. Med.* **73**: 7-12, 1944.
30. Moore, S.: Hyperostosis frontalis interna—preliminary study, *Surg., Gynec. and Obst.* **61**: 345-362, 1935.
31. Moore, S.: Calvarial hyperostosis and the accompanying symptom complex, *Arch. Neurol. and Psychiat.* **35**: 975-981, 1936.
32. Moore, S.: Metabolic craniopathy, *Am. J. Roentgenol.* **35**: 30-39, 1936.
33. Moore, S.: Personal communication.
34. Moreau, M.: Crimes committed by Jacques Pierlot, priest; probable rôle of Stewart-Morel syndrome in causing mental changes, *J. belge de neurol. et de psychiat.* **34**: 458-463, 1934.
35. Morel, F.: L'Hyperostose frontale interne. Syndrome de l'hyperostose frontale interne avec adipose et troubles cérébraux, 1930, Gaston Doin et Cie.
36. Morel, F.: L'Hyperostose frontale interne, *Schweiz. med. Wchnschr.* **67**: 1235-1237, 1937.
37. Mortimer, H.: Discussion of Carr's paper, *Arch. Neurol. and Psychiat.* **35**: 988, 1936.
38. Mortimer, H.: Pituitary and associated hormone factors in cranial growth and differentiation in the white rat: a roentgenological study, *Radiology* **28**: 5-39, 1937.
39. Mortimer, H., Levene, G., and Rowe, E. W.: Cranial dysplasias of pituitary origin, *Radiology* **29**: 135-157 and 279-290, 1937.
40. Mortimer, H.: The influence of the anterior pituitary on cranial form and structure; and the significance of cranial dysplasia in clinical diagnosis, *A. Research Nerv. Ment. Dis., Proc.* **17**: 222-238, 1938.
41. Pende, N.: Krankheitsbilder b. Veränderungen des Schadelinners, München, med. Wchnschr. **84**: 855, 1937.
42. Perkins, O. C., and Bigland, A. M.: Hyperostosis frontalis interna, *Psychiat. Quart.* **12**: 341-350, 1938.
43. Ranson, S. W., Fischer, C., and Ingram, W. R.: Adiposity and diabetes mellitus in a monkey with hypothalamic lesion, *Endocrinology* **23**: 175-178, 1931.
44. Reider, N.: Hyperostosis frontalis interna and degenerative brain disease, *J. Mt. Sinai Hosp.* **5**: 511-516, 1938.
45. Reider, N.: Alzheimer's disease associated with hyperostosis frontalis interna, *Bull. Menninger Clin.* **1**: 123-128, 1937.
46. Roger, A. A.: The internal frontal hyperostosis syndrome with report of two cases, *Canad. M. A. J.* **38**: 129-132, 1938.
47. Roth, N.: The syndrome of internal frontal hyperostosis, *Am. J. Psychiat.* **98**: 63-69, 1941.
48. Ruch, W. A.: Hyperostosis frontalis interna accompanying pregnancy, *Memphis M. J.* **17**: 195-196, 1942.
49. Schiff, P., and Trelles, J. O.: Hyperostosis frontalis of traumatic origin, *Ann. de méd. lég.* **12**: 10-14, 1932.
50. Schneeberg, N. G., Woolhandler, G., and Levine, R.: The clinical significance of hyperostosis frontalis interna, *J. Clin. Endocrinol.* **7**: 624-635, 1947.
51. Schneider, E.: Zur Kenntnis der Schadelosteome und der Hyperostosis frontalis, *Med. Klin.* **32**: 487-490, 1936.
52. Silzer, H. M.: The frontal hyperostosis syndrome, *J. Med.* **19**: 507-510, 1938.
53. Stewart, R. M.: Localized cranial hyperostosis in the insane, *J. Neurol. and Psychopath.* **8**: 321, 1927-1928.
54. Tager, B. N., Shelton, E. K., and Matzen, W. C.: Hyperostosis calvaria interna: its clinical significance, *California and West. Med.* **51**: 384-388, 1939.
55. Timme: Discussion of Carr's paper, *Arch. Neurol. and Psychiat.* **35**: 989, 1936.
56. Van Bogaert, L.: Syndrome of hyperostosis frontalis, *J. de neurol. et de psychiat.* **30**: 317, 1930.
57. Williams, J. W.: Textbook of obstetrics, ed. 5, 1923, D. Appleton & Co., New York, p. 197.
58. Henschen, Folke: Morgagni's syndrome, 1949, Oliver and Boyd, London.

RESPIRATORY FAILURE IN POLIOMYELITIS: A SIMPLE METHOD FOR ITS RECOGNITION AND CONTROL *

By WALTER F. STAFFORD, JR., M.D., and RAMSDELL GURNEY, M.D.,
F.A.C.P., *Buffalo, New York*

THE difficulty in recognizing the imminence of respiratory failure and other pulmonary complications in poliomyelitis results in a shockingly high mortality rate in this disease. When pharyngeal and respiratory muscles are involved, the mortality figures vary from 50 to 100 per cent.¹ If patients can be tided over these often fatal respiratory crises, many will eventually recover sufficient respiratory and other muscle function to carry on a useful life; consequently, it is essential to anticipate and treat these emergencies.

Although unfamiliarity with and fear of respirators may be important contributing factors to the high mortality rate in bulbo-cervical poliomyelitis, an even more important factor appears to be the failure of the clinician to use the respirator soon enough. This delay comes about, it is believed, because of the indefinite criteria advanced for the placement of the patient in the respirator. For example, in the recent publication of the First International Conference on Poliomyelitis,² the following two "definite indications" are offered for the placement of a patient in the respirator: (1) Twitchings around the corners of the mouth, and failure to answer questions. This indication is further qualified by a statement to the effect that the patient should have been placed in the respirator "long before this stage is reached." (2) Breathing difficulty and sleeplessness for two or three nights. It is our opinion that such indications are too vague to be of much assistance.

One purpose of this paper is to emphasize an extremely simple method of acquiring objective criteria which are clearcut indications for use of the respirator. Recognition of impending respiratory failure is readily accomplished by the use of any basal metabolism apparatus capable of measuring vital capacity. With such a machine, a permanent record can be obtained of the rate and depth of breathing, and the maximum possible expiration. Swank³ by such means studied the tidal air and vital capacity in five cases with diminished respiratory function, one of anterior spinal artery thrombosis, and four with multiple peripheral neuropathies. His findings suggest the following four stages in the development of respiratory failure:

1. Reduction of tidal volume and vital capacity to approximately 350 and 1,000 c.c., respectively.

* Received for publication June 12, 1950.

From the Departments of Neurology and Medicine, University of Buffalo School of Medicine and the Buffalo General Hospital, Buffalo, New York.

2. The presence of periodic deep breaths and waxing and waning of the tidal volume.
3. Disappearance of the periodic deep breaths.
4. Disappearance of waxing and waning of the tidal volume, with further reduction of the tidal volume to approximately 200 c.c.

This simple method for the determination of certain aspects of respiratory function which could be used as criteria for the recognition of incipient and advanced respiratory failure seemed especially applicable to patients with poliomyelitis, and was utilized in five adult cases with respiratory involvement. The standard Collins basal metabolism machine was the type at our disposal, and the recordings were made in ink on standard B-R-9 charts.

As in obtaining standard basal metabolic rates, often the first tracing was unreliable because of difficulty on the part of the patient in adjusting to the mouth and nose piece. The difficulty was rapidly overcome as the patient adapted himself to the technic and became less apprehensive.

During the tests, the patients breathed 100 per cent oxygen in order to prevent hypoxemia. Tracings were made during the early stages of respiratory failure, after total respiratory failure had ensued and the patients were in respirators, and during the recovery period. By securing repeated respirograms during these various phases, it was possible (1) to anticipate respiratory failure, (2) to determine, and thus control, the adequacy of ventilation produced by the respirator, (3) to recognize certain pulmonary complications, and (4) to record graphically the return of respiratory function, however slight, as well as to ascertain the length of time the patient could be removed from the respirator without fatigue.

EARLY RECOGNITION OF IMPENDING RESPIRATORY FAILURE

It is a common misconception that respiratory failure in poliomyelitis is a sudden phenomenon, occurring over a matter of minutes. This misconception results from the fact that ordinary clinical observations fail to reveal diminishing respiratory function. In the early phases of respiratory failure, respirations do not appear labored, no cyanosis is present, and the patient is in no discomfort. However, if respirograms are obtained at frequent intervals, changes in the character of the tracing as described by Swank can be detected and will in turn give adequate early warning of impending failure. Consequently, the patient can be placed in a respirator before breathing suddenly ceases or irreversible changes have resulted from inadequate oxygenation of the blood. In addition, if adequate ventilation is restored early by a respirator, atelectasis with all its concomitant effects may be prevented.

The respirograms in figures 1, 2 and 3 illustrate the changes mentioned above. The patient was in no apparent respiratory distress during the

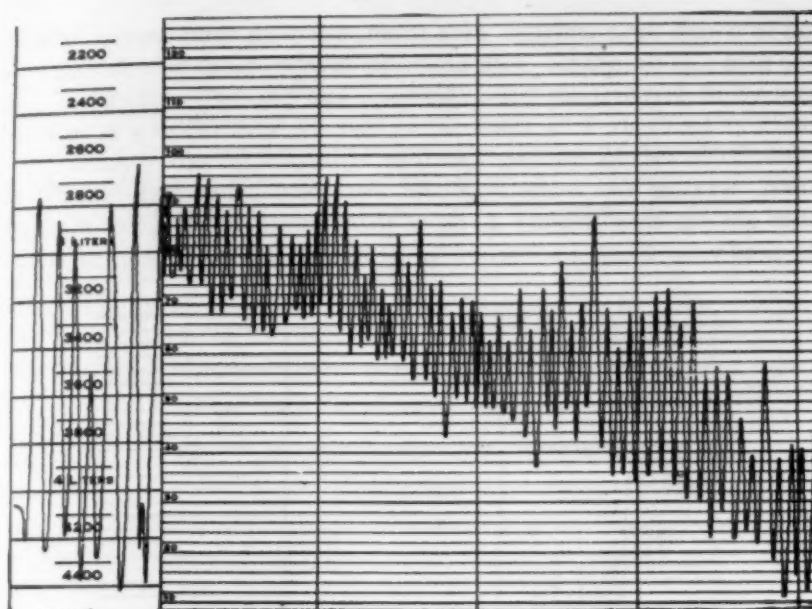


FIG. 1. Time 1:00 p.m. Vital capacity 1700 c.c. Estimated normal for patient, 3,200 c.c. Notice the periodic deep breaths and the waxing and waning of the tidal volume.

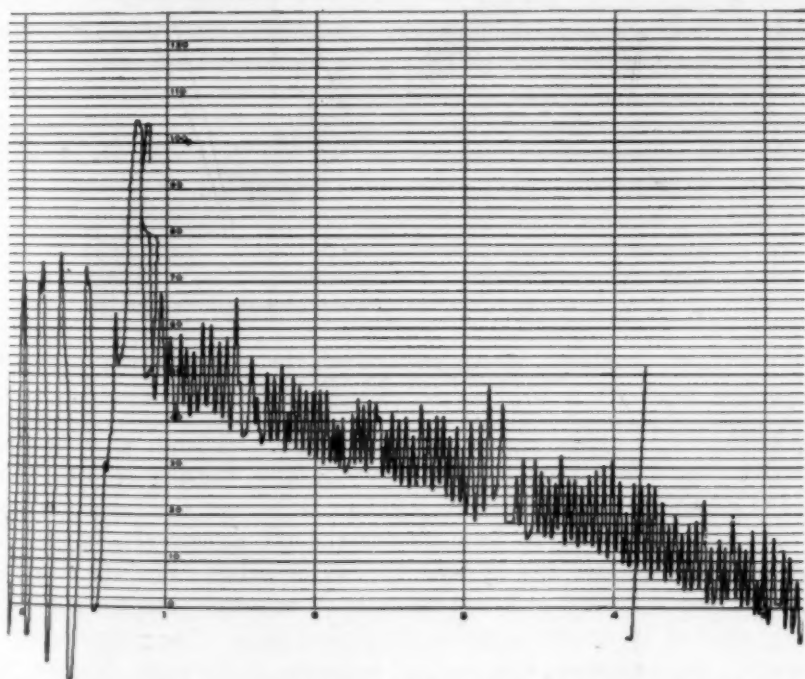


FIG. 2. 4:00 p.m., same day. Average tidal volume diminished and periodic deep breaths diminished in number as well as volume.

period in which these tracings were taken, although symptoms of headache, muscle pain and dysphagia, with abnormal cerebrospinal fluid findings, were suggestive of preparalytic poliomyelitis. The patient's respiratory status, as indicated by figure 1, is abnormal in that the vital capacity is reduced to less than 2,000 c.c., as compared with an estimated normal of 3,200 c.c. In addition, waxing and waning of the tidal ventilation and periodic deep breaths are present. Figure 2, taken three hours later, shows diminution in the tidal volume and a reduction in the number and volume of the periodic

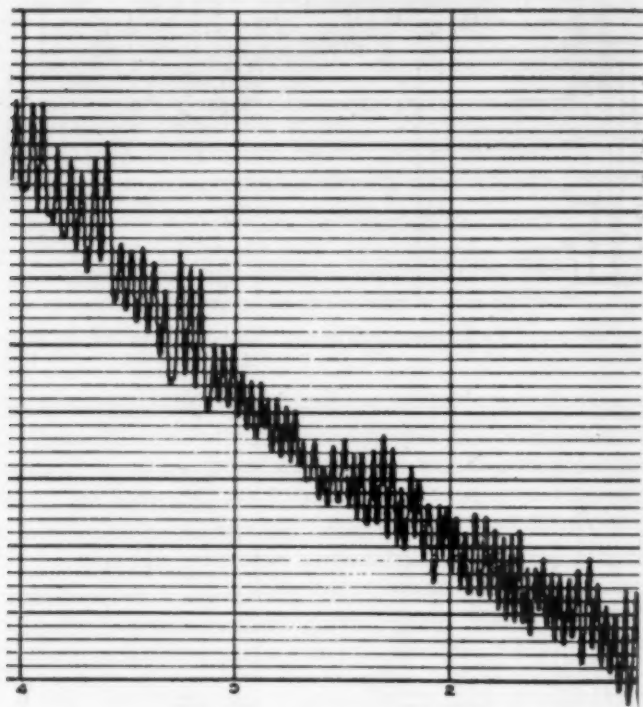


FIG. 3. 6:00 p.m., same day. Average tidal volume now 180 c.c. Periodic deep breaths diminished to 250 c.c. No dyspnea.

deep breaths. In figure 3, at a time when there still were no subjective or objective clinical indications of respiratory distress, the average tidal volume was 181 c.c. and the minute volume 4,175 c.c. at a respiratory rate of 23/min. At this stage, according to Swank's criteria, the patient should have been placed in the respirator, but in order to test the validity of these criteria the respirator was not used until two hours later, at which time the patient was acutely short of breath and complained of chest pain. The patient ultimately recovered, although there was residual weakness of the right shoulder girdle and arm muscles.

ADEQUACY OF VENTILATION IN THE RESPIRATOR

As is well known, artificial respiration improperly administered can be harmful. Hyperventilation will result in hypocapnia, and hypoventilation in anoxia. When a respirator or some other means to replace the normal respiratory function is used for a prolonged period of time, as is frequently necessary in poliomyelitis, it is particularly important to insure optimal ventilation.

There is disagreement in the literature as to what is the optimal tidal volume. The most reliable average figures appear to be those of Mandel Cohen,⁴ who reports an average of 743 c.c. for young healthy males. This is higher than reported in most physiologic textbooks. At any rate, by means of respirograms, accurate measurements can easily be made of the tidal and minute volume of patients receiving artificial respiration, and clinical judgment and blood gas studies assist in determining proper tidal volume for any single patient. One patient was mentally confused at a tidal volume of approximately 450 c.c. By increasing the tidal volume an additional 250 c.c. without change in rate, the confusion disappeared. Arterial oxygen saturation after this increase was 94 per cent.

A mistake easily made is to assume that changes in pressure adjustment of the machine reflect proportional changes in respiratory exchange. A change in negative pressure which will, in one patient, produce a marked variation in pulmonary ventilation, may produce little or no effect in another. For example, by changing the negative pressure from minus 13 cm. H₂O to minus 20 cm. H₂O, the tidal volume of one patient with respiratory muscle paralysis could be increased only 75 c.c., whereas in another patient with comparable paralysis, it could be increased 250 c.c. with a change from minus 13 cm. to only minus 16 cm. H₂O. Hence, in order to determine the effect on the patient's respiratory exchange of changes of negative pressure in the respirator, a respirogram should be obtained frequently.

RECOGNITION OF PULMONARY COMPLICATIONS

Despite the restoration by artificial means of apparently adequate ventilation, pulmonary complications may develop as a result of aspiration, pneumonia and atelectasis. The early recognition of these complications is impossible because the ordinary methods of physical examination of the chest cannot be performed in the respirator. Neither is roentgen-ray examination helpful, because only a small portion of the pulmonary fields can be visualized by this means.

Failure to treat such complications at an early stage may result in permanent alterations in the lungs or death. Frequent respirograms will indicate the presence of these complications before the onset of tachycardia, fever or leukocytosis, the only other indications in a respirator patient of lung complications.

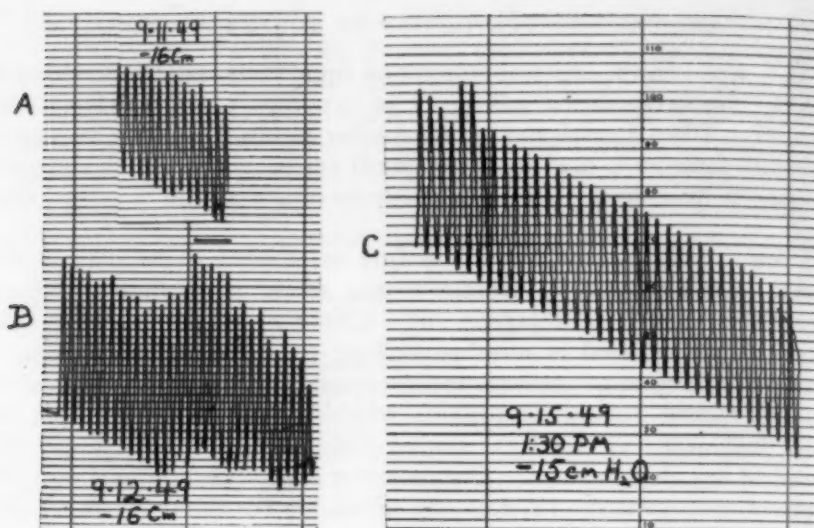


FIG. 4. A—preceding development of atelectasis. B—after development of atelectasis. C—after bronchoscopy.

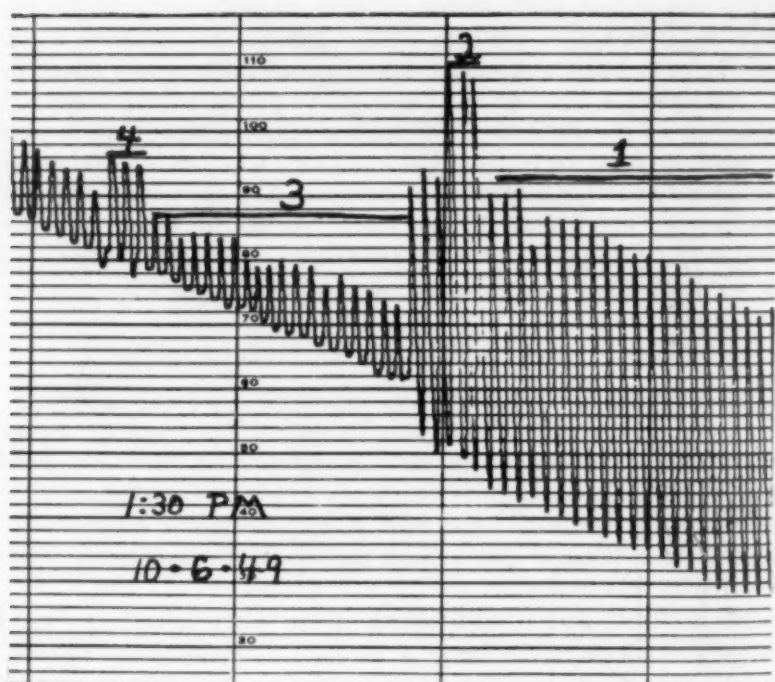


FIG. 5. Atelectasis present. 1. Respiratory excursions with patient in respirator. 2. Voluntary supplementation. 3. Respiratory excursions with patient out of respirator. 4. Vital capacity.

Figure 4 is a graphic record of the ventilation of a patient preceding, during the development of, and following the removal of a mucous plug in the bronchial tree. In comparing tracing B with tracing A, there can be seen in tracing B a marked increase in ventilation with a minute volume increase. However, no breath consciousness was present. Because of the apparent satisfactory clinical condition of the patient, and in the absence of any elevation of temperature or pulse rate, bronchoscopy was postponed for 48 hours, at which time the temperature rose to 101 (39° C.) per rectum, with an elevation of the pulse rate from 90 to 110° F. Tracing C was taken several hours following bronchoscopy at which mucous plugs were

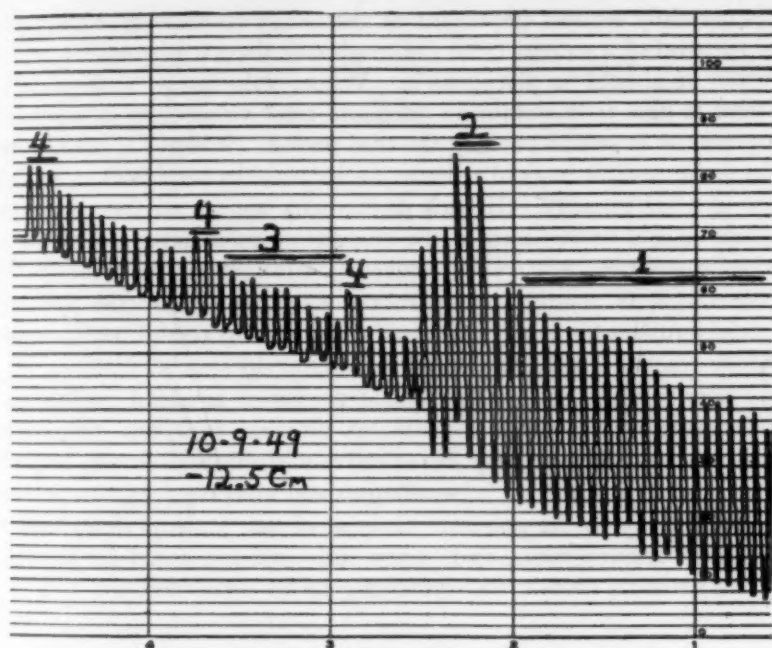


FIG. 6. After bronchoscopy. 1, 2, 3, 4 as in figure 5.

removed from the middle and lower lobe main bronchial segments. On this tracing it can be seen that the minute volume has returned to a quantity comparable to that before the complication occurred. Within 24 hours the temperature and pulse returned to the previous level. There was a similar episode three weeks later with the same sequence of events (see figures 5 and 6). It seems evident that bronchoscopy should be performed as soon as compensatory increase in total volume takes place. Blood gas studies are not helpful at this stage. Oxygen saturation was 94 per cent and $p\text{CO}_2$ was 35 mm. Hg during the stage of hyperventilation.

RETURN OF RESPIRATORY FUNCTION

Unnecessary prolongation of artificial respiration is obviously undesirable. The recognition of return of voluntary respiratory function can be detected quantitatively by the respirogram.

If the patient has any return of voluntary respiratory function he can, by assisting the machine, increase the tidal volume (see figure 5). During the recovery stage, respirograms appear to indicate a reversal of the phases undergone during the development of respiratory paralysis. Tidal volume increases to the point that adequate oxygenation of the blood can be maintained. Following this, a slight reserve, i.e., vital capacity, becomes evident, and as recovery progresses this increases in amount.

It is certainly no less important at this stage to determine the optimal time of removal of a patient from the respirator than it was earlier to determine when he should be placed in it. When, voluntarily, without fatigue, the patient is able to maintain an adequate tidal volume, as determined by respirograms, it is safe to prolong the trial period. Fatigue is readily recognized by a diminution in tidal volume, an increase in respiratory rate, and a decrease in vital capacity. If such phenomena appear on the respirogram, the patient should be replaced in the respirator immediately. In this way, acute respiratory failure as well as unnecessary fatigue can be avoided. With these criteria, it is possible to measure the length of time the patient can adequately ventilate his lungs voluntarily, and also to record improvement in respiratory reserve which may occur steadily or in steplike fashion.

Any patient undergoing a prolonged period of artificial respiration becomes depressed and concerned about his ultimate recovery. Such understandable discouragement may be effectively combated, in the experience of the authors, if an increase in ventilation and vital capacity can be demonstrated graphically to the patient. Several of our patients demanded a report on their respirograms, and, when improvement could be shown, the rise in the patient's morale was gratifying to all concerned.

SUMMARY

1. A simple, graphic method of evaluating certain aspects of respiratory function in poliomyelitis is presented.
2. By the use of this method it is possible to anticipate respiratory failure before it is evident clinically.
3. The necessity for measuring tidal and minute volumes during artificial respiration is emphasized.
4. During artificial respiration, pulmonary complications can be demonstrated by this method before any recognizable clinical signs are present.
5. This method gives a satisfactory indication of return of respiratory function and serves as a guide for evaluation of the patient's ability to withstand removal from the respirator.

BIBLIOGRAPHY

1. Authors' material (50 per cent—12 cases) and personal communication (100 per cent—10 cases).
2. Poliomyelitis. Papers and discussion presented at the First International Poliomyelitis Conference, Philadelphia, J. B. Lippincott Company, 1949, p. 131.
3. Swank, R. L.: Respiratory impairment and pulmonary complications in paralyzed states, *Ann. Int. Med.* 32: 229-242, 1950.
4. Cohen, M. E.: Quoted in Swank, R. L., and Smedal, M. I.: Pulmonary atelectasis in stuporous states; a study of its incidence and mechanisms in sodium amytal narcosis, *Am. J. Med.* 5: 210, 1948.

NOTES ON A SYMPOSIUM: THE INTERNIST AS A PSYCHIATRIST *

By STEWART WOLF, M.D., and HAROLD G. WOLFF, M.D., F.A.C.P.,
New York, N. Y.

FIFTY years ago in the education of an internist, emphasis rested most heavily upon the teaching of pathology. Since then there has been leading emphasis on physiology and, later, bacteriology. These three disciplines are no less important than they ever have been in the education of a competent internist, but it is becoming increasingly clear that since psychologic phenomena are a part of the problem of every patient for whom he cares and are of leading importance in 40 to 60 per cent of his patients, the internist also needs understanding and skill in the technics of psychiatry.

In order adequately to apply these technics, the physician must have certain personal qualifications—an interest in and sympathy with people and their problems of adaptation. More than that, he must believe in their potential for a more constructive adjustment. He needs to be able to "give out" encouragement and support, even in the face of the patient's hostility. It is an experience of everyday practise and part of the therapeutic process that the patient expresses vicariously toward the physician in various direct and indirect ways the hostility he feels toward parents, wife or boss. The physician needs patience. He must be willing to be anxious, to carry responsibility while his patient is slowly working through misinterpretations and poor decisions to a better adjustment. He must often worry along with little progress or settle for a limited objective, realizing that rejecting the patient or giving him up as a bad job would be destructive. The physician must be willing to listen, and to afford the time and energy which that requires. Finally, the physician needs restraint. He must be particularly careful not to express contempt, ridicule or disapproval, directly or indirectly, by word or gesture. He must avoid pressing a course of action which the patient may not be able to accept, however obvious it may seem to the physician. Especially, he must assiduously avoid unconsciously using his patient to work out his own problems and conflicts, or dominating him to enhance his own feeling of security.

Apart from these personal qualifications, the physician requires some sort of systematic interest in and experience with human nature. He must know how to approach and interview a patient. He must know the significance of blocking, of projections and associations. He must understand the methods of classification of neuroses and psychoses, and he must know something of psychopathology and psychodynamics.

* Panel discussion presented before the American College of Physicians in Boston, Mass., on April 18, 1950. Other participants were Dana W. Atchley, Eric Lindemann, Henry M. Thomas, Jr., William H. Dunn and Johannes J. Groen.

From the Departments of Medicine and Psychiatry of Cornell University Medical College and the New York Hospital, New York.

In therapy, just as he must know the signs of digitalis intoxication, so he must know the signs of over-exploration, evidences of impending panic, disorganization or serious depression. These signs are recognizable, reasonably clear-cut, and just as readily learned by the inquisitive medical student as are the signs of overdosage of a drug.

It is not in the scope of this summary to suggest the specific curricular changes which are needed so that the medical student can be properly educated in these matters. Suffice it to say that curricular modifications are needed, since it is fairly clear that the student prepared to graduate from medical school today is often not prepared to evaluate his medical patient as a person. He does not take a history which yields information concerning the patient's experiences, attitudes and reactions. He may have been taught to do it in his courses in psychiatry, but to him it is a psychiatric history, not a medical history.

Among the sources of information available to the physician in building his formulations are, first, the direct statements of the patient, either spontaneous or in reaction to questions; next, the unintentional verbal implications which the patient gives. For example, when a woman was asked, "Tell me about your husband," she replied, "Well, he's the finest person in the world and I couldn't have a better husband." She was then asked, "What is there about him which impresses you so?" She replied, "Well, he's so neat about the way he puts his socks away in the top drawer." An experienced observer would recognize such "damning with faint praise" as an indication of suppressed or repressed hostility towards the husband. He would have learned that this sign is nearly as definite as a presystolic rumble in indicating mitral stenosis. Hundreds of such unintentional verbal implications come out when an individual is describing something. Then there are the implications of gesture and behavior which are available to the physician and which again very often indicate not only things which the individual does not intend others to know but things of which the individual himself is unaware, his unconscious mental processes. Dreams and free associations are similarly useful in gathering unconscious or partly conscious data. In addition, an often neglected source of information about a patient is the knowledge of the cultural and social pressures surrounding him. Finally, one of the most valuable methods of gathering information is by watching the individual's performance and reactions in day to day living.

With regard to therapy, it is important to realize that every contact which the physician has with the patient has therapeutic implications. Types of therapy cannot be classified adequately because a therapy cannot be used in a pure culture. Neither can one distinguish, from a methodologic viewpoint, deep from superficial therapy. The term "deep" refers to a therapy which helps the patient to a reorientation toward himself and the people close about him and to a more constructive and mature way of

dealing with his day to day problems. This is occasionally achieved by the briefest sort of contact with a particular individual, without much being said, or it may fail to be achieved after five years of painstaking analysis.

It is currently popular to distinguish between suppressive therapy, on the one hand, and expressive, on the other. It is, however, no more possible to make a categorical distinction between these than between other loosely descriptive terms. In suppressive therapy, the emphasis is put on building the patient's confidence and on exploiting all possible sources of satisfaction in the patient's life. In this way it is hoped that the destructive effects of unconscious conflicts will be proportionately minimized. In expressive therapy, the emphasis is on uncovering repressed material so that the patient can face the issues in perspective. Thus he may realize that powerful childhood conflicts need no longer apply to his scheme of life and, with the help of his relationship with the therapist, he may "grow up" and achieve a greater degree of emotional maturity.

Realizing that one cannot employ one method to the exclusion of others the following descriptive categories are offered as examples of where emphasis can be placed in the therapeutic process.¹

Reassurance and emotional support have been shown in an earlier study to be the most powerful and universally applicable therapy. This therapy derives from the human warmth of the physician and is directed toward enhancing the strength, faith and determination of the patients, as well as toward releasing inhibitions and repressions. It implies an understanding and tolerant attitude on the part of the physician and includes recognition and praise for the assets and achievements of the patient. It also involves an unswerving interest in and concern for whatever problem or question the patient brings to the doctor. In short, without becoming too identified with the patient's problems, the physician attempts to play the rôle of a strong, authoritative (but not authoritarian), thoroughly dependable friend of the patient.

Free verbal expression of conflicts and feelings is directed toward promoting a release of tension, and often results in relief from anxiety and resentment and lessens the need to act out emotional conflicts in a socially undesirable manner. It has also often been found that the free expression of their conflicts has not only given patients a sense of relief, but has promoted understanding and the gaining of perspective.

Advice regarding attitudes, habits and activities must be undertaken cautiously, but usually the patient can be encouraged to discuss the advantages and disadvantages of a given situation before making important decisions. Thus, helping him to take independent action may lead to the development of a greater feeling of security and capacity to deal with ensuing problems. However, at times when the patient is deadlocked, the weighting of the scales by the preference of the physician, expressed or implied, is helpful. Such advice, coming from a physician, relieves the pa-

tient of responsibility and guilt, enabling him to make constructive decisions which might otherwise have been delayed indefinitely.

Explanation of the physiologic processes involved is almost always helpful in dispelling the patient's fear that the doctors believe his symptoms to be imaginary. Often there is little or nothing known of the mechanisms behind the symptoms, but it is important for the patient to realize that the doctor considers the symptoms bona fide. When the mechanisms are known or can be explored, great benefit can come from enabling the patient to see and test the relationship between events, attitudes and bodily disturbances.

The physical examination and diagnostic procedures constitute important therapy in themselves, not only from the standpoint of ruling out ominous diseases, but because they reflect the serious concern and thoroughness of the physician. In this connection it is important that new symptoms which appear in the course of treatment receive equally serious and detailed attention.

Interviews with other members of the family may lead to improvement in interpersonal relationships and decrease in anxieties and resentments in the home. Often it is possible thereby to make concrete changes in the life situation which remove a significant number of stressful factors. Often important light on the patient and his development is cast in the physician's contacts with other members of the family. This information can be used in later therapeutic sessions with the patient.

An analysis of the emotional development during infancy, childhood and adult life may be elicited by a biographic review and also by asking the patient to associate freely about significant life events and his reactions to them. Recall and interpretation of dreams through spontaneous association by the patient facilitates the uncovering of emotional conflicts. The feeling of security engendered by this process and the release of emotional repression aid in establishing healthier patterns of bodily function and in the development of more mature attitudes and behavior.

Frequently, considerable improvement may be achieved without the verbal expression of insight. Many patients who appear to have developed some comprehension of the dynamics of their illnesses express it rarely or not at all. In most cases it does not appear that such an admission is essential to a good therapeutic result.

Usually sedative drugs can be used sparingly to afford symptomatic relief or to tide the patient over a difficult period in his illness, but their use should be discontinued as soon as possible.

Utilizing all of these methods, it has been shown that the well trained internist who has some background in psychiatry can offer satisfactory and definitive treatment to patients with so-called psychosomatic disorders. Groen,² for example, in a direct comparison of effectiveness in ulcerative colitis of psychotherapy administered by an internist and a psychiatrist,

found no significant difference. Dunn³ has also observed that properly qualified internists can offer effective and definitive psychotherapy to their patients. In comparing a medical with a psychiatric out-patient clinic, Dunn noted more defensiveness on the part of the patients in the psychiatric clinic, partly because of the customary fear that the psychiatrist will "probe their innermost secrets," and partly because of resentment born of a feeling that their physician, in sending them to a psychiatrist, has considered their symptoms "imaginary." Dunn also gained the impression that the detailed physical examinations and evaluation accorded to the patients in the medical clinic "made for a much more confidential relationship initially between patient and physician." Thus, as one does not need to be a biochemist to treat a patient with insulin or curare, and one does not need to be a bacteriologist to prescribe diphtheria toxoid or aureomycin, so one does not need to be a psychiatrist to give definitive psychotherapy. Atchley⁴ has referred to internal medicine as the only specialty which is clearly committed to a consideration of the whole patient. It does not seem impossible that the internist can become a whole doctor.

The authors are grateful to Dr. Herbert S. Ripley for help in formulating the categories of treatment.

BIBLIOGRAPHY

1. Ripley, H. S., Wolf, Stewart, and Wolff, H. G.: Treatment in a psychosomatic clinic, *J. A. M. A.* 138: 949, 1948.
2. Groen, Johannes J.: Data to be published.
3. Dunn, William H.: Personal communication.
4. Atchley, Dana W.: Personal communication.

CASE REPORTS

SUBACUTE BACTERIAL ENDOCARDITIS DUE TO *STREPTOCOCCUS FECALIS**

By BEN ZWEIFLER, M.D., Brooklyn, N. Y., ELI SAR, M. D., New York, N. Y.,
and ISIDORE FEDER, M.D., F.A.C.P., Brooklyn, N. Y.

SUBACUTE bacterial endocarditis caused by *Streptococcus fecalis* has always presented a problem in therapy. This organism, together with *Str. liquefaciens*, beta *Str. symogenes*, and beta *Str. hemothermophilus*, belongs to the Enterococcus group of Sherman. They are part of Group D, in Lancefield's classification of streptococci. A review of the literature reveals varying degrees of therapeutic success with both streptomycin and penicillin. Tumulty and Harvey,¹ in their review of 35 cases of subacute bacterial endocarditis, state that *Streptococcus fecalis* manifested the highest degree of penicillin resistance, a resistance which became progressively greater as treatment progressed. In their group both patients infected with this organism died. Keefer et al.² pointed out that *Streptococcus fecalis* is one of the organisms most resistant to streptomycin therapy. They state that the development of resistance of the infecting organism to streptomycin occurs rapidly when all infecting organisms are not eliminated. Cady and Allen³ reported one of the earliest cases of subacute bacterial endocarditis due to *Str. fecalis* which was treated with streptomycin. They concluded that their therapy was unsuccessful because of inadequate supplies of streptomycin, and postulated that larger dosage would have proved efficacious. Guss⁴ reported a case that did not respond well clinically to penicillin. In a sensitivity test the organism showed resistance to a penicillin concentration of 5 units per c.c. However, a 20 day course of streptomycin therapy resulted in a cure. The treatment of four cases of subacute enterococcus endocarditis was reported by Sirota et al.⁵ One case received two courses of streptomycin therapy, totaling 20 gm. and 41 gm. respectively, but no cure was effected. A cure was attained in another patient by two courses of penicillin therapy, 200,000 units daily by intravenous drip for 28 days, and 500,000 units daily for one month, respectively. Failure was reported in a case that, in addition to massive sulfonamide therapy and penicillin, received as a last course 10 million units of penicillin intramuscularly daily for 35 days. The authors concluded that the resistance of the organism had increased after the course of therapy. The fourth case, in addition to a course of sulfadiazine, received 600,000 units of penicillin daily for four weeks (500,000 units by continuous intramuscular drip and booster doses of 50,000 units intramuscularly twice daily), but terminated fatally. Harris's⁶ patient received two courses of penicillin therapy, totaling over 24 million units. The patient was cured despite a *Str. fecalis* organism that was resistant to a concentration of 10 units of penicillin per cubic centimeter.

* Received for publication November 11, 1948.

From the Department of Medicine, Beth-El Hospital, Brooklyn, New York.

The case report that follows describes the therapy in our case of subacute bacterial endocarditis due to *Streptococcus fecalis*. Treatment was initially instituted with streptomycin. When the organism developed resistance to streptomycin and positive blood cultures recurred, penicillin and caronamide were successfully utilized to bring about a cure.

CASE REPORT

A 20 year old unmarried colored female was admitted to the Beth-El Hospital on April 26, 1948. Three days before admission she had developed severe pains in the lower back and over the region of the right buttock and hip, and a generalized headache. She complained of occasional "shooting pains" in her ankle joints. On the day preceding hospitalization, pains in the knee joints appeared. She "felt feverish" but no temperature was taken. A physician prescribed salicylate powders but the joint pains did not abate.

Past history disclosed an attack of acute rheumatic fever at the age of five with occasional bouts of palpitation and swollen joints since that time. Otherwise the past history and system review were noncontributory.

Physical examination revealed a young colored female appearing acutely ill. The admission temperature was 101° F.; pulse, 130; respirations, 18, and blood pressure, 118 mm. Hg systolic and 70 mm. diastolic. The head, eyes, ears, and nose were essentially negative. Both tonsils were hypertrophied. The mouth contained many carious teeth and the oral hygiene was poor. No cervical adenopathy was present, but there was resistance to flexion of the neck, which was felt to be occasioned by the severe lower back pain. The heart sounds were regular, rapid and of good quality. A loud systolic murmur was heard over the apex. The lungs were clear to percussion and auscultation. The abdomen presented no abnormal findings. The liver, spleen, and other organs could not be felt. The lumbar spine was extremely tender to palpation. A more detailed examination of the spine could not be made on admission. The right knee was swollen and warm to palpation, and flexion caused excruciating pain. Two days later, after salicylates by mouth, the swelling and joint pains had regressed markedly. Tenderness over the right buttock with severe muscle spasm was present. Examination of the spine was still unsatisfactory, but no point tenderness could be elicited. Digital rectal examination was negative. A proctoscopic examination nine days after admission was negative. A satisfactory pelvic examination was not possible until the twenty-second hospital day, when it was performed with the aid of intravenous pentothal anesthesia with negative findings.

The initial laboratory findings were as follows: red blood cells, 3,640,000; hemoglobin, 67 per cent; platelets, 490,000; white blood cells, 6,000, with 63 per cent segmented neutrophils, 6 per cent staff neutrophils, 28 per cent lymphocytes, and 5 per cent monocytes. No sickle cells were seen in a 24 hour wet preparation. Analysis of a casual specimen of urine disclosed a specific gravity of 1.010; 1 plus albuminuria, and 30 to 40 white blood cells per high power field. A catheterized specimen taken three days later showed a specific gravity of 1.022, was negative for albumin and sugar, and contained 1 to 2 white blood cells per high power field. The sedimentation rate was 16 mm. in one hour by the Wintrobe method. The blood sugar, urea nitrogen and total protein were well within normal limits. A blood Kline test was negative. An antifibrinolysin titer was 3 plus. Blood agglutination tests for typhoid, paratyphoid A and B, *B. proteus* OX19, and *B. abortus* were all within the normal dilution range. Smears and cultures from the vagina, cervix and Skene's glands were negative. A culture of the mouth revealed *Micrococcus catarrhalis* and pneumococcus organisms. A chest roentgen-ray showed the heart to be of the ovoid type and moderately enlarged. Roentgenograms showed distention

of the capsule of the right hip joint, suggesting the presence of an increase in fluid. The right knee showed a moderate distention of the patellar ligament, indicative of a moderate increase in intracapsular fluid. Repeated electrocardiograms revealed sinus tachycardia, left axis deviation, and changes indicative of slight myocardial damage. The P-R interval was normal.

On April 29, a blood culture taken two days earlier was reported positive. The organism was a gram-positive enterococcus that was subsequently identified as *Streptococcus fecalis*. Blood cultures repeated on April 28, April 29, May 1, May 3, and May 6, were all reported positive for *Streptococcus fecalis*, the number of colonies ranging from 7 to 65 per c.c. of blood. During the first 12 hospital days, the patient ran a temperature ranging from 100° to 103° F. Marked tenderness on palpation of the soft tissues about the right buttock persisted constantly, and did not regress for another three weeks.

On May 7, sensitivity tests were performed with streptomycin. Growth of the autogenous enterococcus organism was not inhibited by 0.05, 0.2, 0.5, 2, 4, 6, and 8 units per cubic centimeter of blood. Growth was inhibited by 16 units per cubic centimeter of blood. With penicillin, growth of the organism was not inhibited by 0.04, 0.1, 0.25, 2, 4, and 8 units per cubic centimeter. Tests with higher concentrations of penicillin were not performed at this time.

Streptomycin therapy, 0.5 gm. intramuscularly every three hours, was started on May 7. Negative blood cultures were obtained on May 8, 10, 11, 12, 13, 15 and 17. However, a low grade temperature up to 100.4° F. persisted. On May 15, a needle aspiration over the area of maximal tenderness in the right buttock was productive of 1 c.c. of serosanguineous fluid. A culture of the aspirated fluid was positive for *Streptococcus fecalis* three days later. On May 20, 13 days after the start of streptomycin, a blood culture was taken which four days later revealed two to three enterococcal colonies per cubic centimeter. On May 24, the right buttock was incised, some necrotic tissue was removed, and a catheter left in situ for drainage and local instillation of streptomycin. The streptomycin dosage was raised to .75 gm. intramuscularly, every three hours and .25 gm. was instilled through the catheter every four hours. The catheter was removed two days later. The buttock wound subsequently healed, and all pain, tenderness and muscle spasm were completely relieved. On May 25, giant urticaria appeared on the left thigh and, in addition, puffiness of the face was present. Benadryl, 100 mg. three times a day, was administered for two days. The urticaria and facial edema disappeared in one day. Blood cultures taken on May 26 and 27 were reported positive two days later. On May 28, severe tinnitus occurred. Blood cultures taken on May 28 and June 3, were positive three days later, the latter revealing 15 to 20 colonies per cubic centimeter. On June 3, the streptomycin dose was increased to 1 gm. intramuscularly every three hours. For the following two days, the temperature ranged between 100° F. and 101° F., and the blood cultures still remained positive.

The *Streptococcus fecalis* organism obtained from the last positive blood culture was retested for penicillin sensitivity and found to be resistant up to 8 units per cubic centimeter of blood. However, the organism was sensitive to 16, 32 and 64 units per cubic centimeter. A sulfadiazine sensitivity test disclosed resistance up to 2.5 mg. of sulfadiazine per cubic centimeter of blood. On June 5, streptomycin therapy was discontinued and penicillin therapy was instituted, with a dosage regime of 1,250,000 units intramuscularly every three hours (10,000,000 units per 24 hours). Caronamide, 4 gm. every four hours, was started on June 14 and continued for the remainder of the course of penicillin therapy. On June 28, a blood specimen taken two hours after an injection of penicillin revealed a blood level between 16 and 32 units per cubic centimeter. On July 6, a blood specimen taken three hours after an injection of penicillin revealed a level of 1 to 2 units per cubic centimeter. Negative

blood cultures were obtained on June 7, 8, 9, 10, 11, 14, 16 and 21, and on July 2, 7, 9, 19, 23 and 30. The patient became afebrile 24 hours after the institution of penicillin therapy and remained afebrile throughout the entire course of therapy, with two exceptions. On one occasion, after three weeks of therapy, she ran a temperature of 100° F. on two successive evenings. At this time the patient had tenderness and induration over all injection sites. On the thirty-third day (July 7, 1948) of penicillin and caronamide therapy, a papular rash appeared on the face, chest and lower extremities. The temperature rose to 104° F. and remained for the most part above 102° F. for three days. Benadryl, 100 mg. every four hours, was administered without improvement. Penicillin and caronamide were discontinued on July 9, the thirty-fifth day of therapy.

During the entire course of caronamide administration, a persistent 3 plus albuminuria was present. On repeated concentration tests of the urine during this time, the specific gravity was never higher than 1.011. Following the termination of therapy, the albuminuria ranged from zero to a trace. Impaired concentration of the urine was still present on discharge. A persistent pyuria, ranging from 10 to 60 white cells per high power field on noncatheterized specimens, was attributed to a moderate nonspecific leukorrhea. Occasionally, 2 to 5 red cells were found in the urine. Repeated blood chemistries that included total protein, A/G ratio, urea nitrogen and uric acid were well within normal limits. The systolic mitral murmur became higher pitched and shriller during the hospital stay.

Roentgen-ray examination of the teeth showed the presence of retained root fragments of the left lower molar region with abscesses. On July 21 the patient was again placed on a regime of 10,000,000 units penicillin daily and 4 gm. of caronamide every four hours, preparatory to dental extraction. The lower left first molar roots were extracted July 22. The following day the patient complained of generalized pruritus. Urticarial spots were present on both buttocks. Benadryl, 100 mg. four times a day, was given without relief. On July 23 the caronamide was discontinued and the complaints of pruritus ceased promptly. A right lower molar root fragment was extracted on July 28. A culture from the root socket revealed *Micrococcus catarrhalis* and *B. coli*. No gram-positive organisms were found.

On July 31 penicillin was discontinued and the patient was discharged from the hospital.

Following discharge she has been followed through our out-patient department. Blood cultures were taken once a week for two weeks, and have been taken twice a month up to the present time. All blood cultures are negative. Additional renal function tests were performed and revealed the following: Fishberg concentration test showed specific gravities of 1.004, 1.019, and 1.016. A urea clearance test disclosed a 100 per cent average normal function. A phenolsulfonphthalein test revealed a 9 per cent dye excretion in one hour and 40 per cent in two hours. A repeat phenolsulfonphthalein test done one week later revealed a 24 per cent dye excretion in one hour and 42 per cent in two hours. There has been no albuminuria, and microscopic examination of the sediment has been negative.

DISCUSSION

The resistance of the infecting *Str. fecalis* organism in our case to 8 units per cubic centimeter of blood of both penicillin and streptomycin and to 2.5 mg. sulfadiazine per cubic centimeter of blood in vitro posed the problem of selection of the proper antibiotic agent. In view of the experience of Tumulty and Harvey¹ that a more effective antibiotic than penicillin is needed to treat *Str. fecalis* endocarditis, we started with streptomycin, following the recommendation of Hunter² regarding dosage. The blood cultures remained sterile for 12 days. With the

reappearance of positive blood cultures, the dosage was increased from 4 gm. to 6 gm. and finally to 8 gm. daily. A total dosage of 138 gm. (138 million units) was administered intramuscularly. Four grams (4 million units) were instilled locally through the drainage tube in the right buttock. However, blood cultures still remained positive. It then became apparent that the infecting organism had become resistant to streptomycin, and that another therapeutic agent was indicated. Upon retest of sensitivity it was found that the organism did not grow in a concentration of 16 or more units of penicillin per cubic centimeter of blood. At this time our attention was directed to the work of MacNeal, Blevins, and Poindexter,⁸ who obtained an arrest in a case of enterococcal endocarditis with the combined use of penicillin and enterococcus bacteriophage. These authors felt that *Str. fecalis* strains were usually susceptible to lysis by enterococcus bacteriophage. Miss A. Blevins, of the Department of Bacteriology of the New York Postgraduate Hospital, kindly prepared an enterococcus bacteriophage that had a good lytic activity on the *Str. fecalis* organism of our patient. Nevertheless, it was decided to hold the bacteriophage in abeyance unless massive doses of penicillin alone could not effect a cure. Because Crosson et al.⁹ have pointed out that the penicillin plasma concentration can be enhanced two- to sevenfold by the oral administration of caronamide, 4 gm. were administered every four hours in conjunction with the penicillin.

Two days following the institution of penicillin therapy, 10 million units daily, the blood culture became sterile. Intramuscular injections every three hours were employed because, according to Jones and Tichy,¹⁰ there is no significant difference in the percentage of cures with continuous intravenous drip therapy. Penicillin was administered for 35 days. A total dosage of 350 million units of penicillin and 600 gm. of caronamide was administered. Blood cultures immediately became sterile and remained so to date. The patient is clinically well.

With the demonstration of abscessed root fragments, the therapeutic regime of Glasser et al.¹¹ was followed. The roots were extracted and penicillin, 1,250,000 units every three hours, was administered prior to and for three days following the extractions. A total dosage of 100 million units of penicillin and 72 gm. of caronamide was administered for this purpose.

Complicating factors such as embolic phenomena, cardiac and renal insufficiency, acute rheumatic fever and sensitivity to penicillin, profoundly affected the course and results of cases in Tumulty and Harvey's series.¹ Although complications occurred in our case, we were fortunate in that they did not interfere with our course of treatment or with the final result. Marked albuminuria and diminished concentrating function of the kidney were apparently a caronamide effect. Although the albuminuria has completely cleared, the low specific gravity of the urine is still evident. This, however, also appears to be correcting itself. At no time was there any disturbance in the blood chemistry to indicate renal insufficiency.

The persistent pain in the right buttock during the early weeks of illness and subsequent culture of the organism from the aspirated fluid posed a problem for us. Was this the primary source of the infection or was it a secondary focus due to embolization? Gynecologic and proctosigmoidoscopic examinations were negative. We are inclined to feel that this was perhaps the result of an embolic episode. Incision and drainage and instillation of streptomycin effected a complete cure.

The joint pains and swelling in conjunction with electrocardiographic changes and the positive antistreptolysin titer may have been indications of active rheumatic fever. Although salicylates promptly relieved the joint manifestations, they had no effect whatsoever on the clinical course of the bacterial endocarditis.

Systemic reactions to both streptomycin and penicillin were well controlled with benadryl. Local reactions, as evidenced by pain, induration and fever, could not be avoided. Nevertheless, we feel that the constant intravenous administration of such massive doses of penicillin would also have been attended with objectionable side effects.

We can stress with others the absence of such classical signs of subacute bacterial endocarditis as an enlarged spleen, petechiae in the skin or mucous membranes, red blood cells in the urine, etc. One need not place too much reliance on such findings to establish the diagnosis.

SUMMARY

1. A case of subacute bacterial endocarditis due to *Streptococcus fecalis* is presented. The literature pertaining thereto has been reviewed.

2. Streptomycin therapy was instituted. After 12 days of treatment, during which the blood cultures remained sterile, positive blood cultures were again obtained. This indicated the development of resistance to this antibiotic. Larger doses were then employed for 17 more days. A total of 138 gm. was thus given but blood cultures still remained positive.

3. Penicillin, 10 million units given intramuscularly daily for 35 days (350 million units), in conjunction with caronamide orally (600 gm.), resulted in a cure.

4. Complications present before and arising during therapy have been noted.

CONCLUSION

Adequate dosage of penicillin given for an adequate period of time, in the absence of fatal complications, can completely cure subacute bacterial endocarditis due to *Streptococcus fecalis*.

BIBLIOGRAPHY

1. Tumulty, P. A., and Harvey, A. M.: Experiences in the management of subacute bacterial endocarditis treated with penicillin, *Am. J. Med.* **4**: 37 (Jan.) 1948.
2. Keefer, C. S., Blake, F. G., Lockwood, J. S., Long, P. H., Marshall, E. K., and Wood, W. B., Jr.: Streptomycin in the treatment of infections, *J. A. M. A.* **132**: 70 (Sept. 14) 1946.
3. Cady, J. B., and Allen, W. H.: A case of *Strep. fecalis* subacute bacterial endocarditis treated unsuccessfully with streptomycin, *Guthrie Clin. Bull.* **16**: 31 (July) 1946.
4. Guss, J. H.: Successful treatment of subacute bacterial endocarditis with streptomycin, *Am. Heart J.* **35**: 662 (April) 1948.
5. Sirota, J. H., Gerber, L. E., and Baehr, G.: Chemotherapy of subacute enterococcus endocarditis, *J. Mt. Sinai Hosp.* **14**: 604 (Sept.-Oct.) 1947.
6. Harris, R.: Subacute bacterial endocarditis: report of enterococcal infection treated with penicillin, *Bull. New York M. Coll., Flower and Fifth Ave. Hosps.* **8**: 61 (Oct.) 1945.
7. Hunter, T. H.: Use of streptomycin in the treatment of bacterial endocarditis, *Am. J. Med.* **2**: 436 (May) 1947.

8. MacNeal, W. J., Blevins, A., and Poindexter, C. A.: Clinical arrest in enterococcus endocarditis, *Am. J. M. Sc.* **211**: 40 (Jan.) 1946.
9. Crosson, J. W., Boger, W. P., Shaw, C. C., and Miller, A. K.: Caronamide for increasing penicillin plasma concentrations in man, *J. A. M. A.* **134**: 1528 (Aug. 30) 1947.
10. Jones, S. H., and Tichy, F.: Bacterial endocarditis treated with penicillin, *New England J. Med.* **236**: 729 (May 15) 1947.
11. Glasser, R. J., Dankner, A., Mathes, S. B., and Harford, C. G.: Effect of penicillin on the bacteremia, following dental extraction, *Am. J. Med.* **4**: 55 (Jan.) 1948.

CANDIDA ASTHMA *

By EDMUND L. KEENEY, M.D., F.A.C.P., San Diego, California

BRONCHIAL asthma, due in turn to a bronchial infection from *Candida* (*Monilia*) *albicans*, has never been recorded in the medical literature. It is the purpose of this report to call to the attention of the medical profession that a bronchial infection from *Candida albicans* can provoke asthmatic manifestations of hypersensitivity, and that the bronchial infection and the asthmatic symptoms can apparently be cured by the persistent use of an aerosol of sodium caprylate.

The use of *Candida* as the generic name of this yeastlike fungus to replace the familiar, but invalid, *Monilia* cannot be justified by priority or frequent past usage. However, at the Third International Microbiological Congress in 1939, those delegates interested in the subject agreed to use *Candida*, and most workers in the field of mycology have accepted the decision. It would be well for bacteriologists and medical men to abide by this decision in the interests of uniformity. With this in mind, I have chosen to identify, succinctly, bronchial asthma due to *Candida albicans* as "*Candida* asthma" and not as "*Monilia* asthma."

It has been demonstrated previously that the sodium salt of caprylic acid inhibits in vitro the growth of *Candida albicans*,^{1,2} and also that sodium caprylate applied locally has been effective in the treatment of cutaneous infections due to this organism.³ With the present interest in aerosols as a means of introducing chemical agents into the respiratory tract, it was reasonable to predict that sodium caprylate aerosol might act effectively in the treatment of a bronchial infection due to *Candida albicans*.

CASE REPORT

History: The patient, a 37 year old insurance salesman, first consulted me 16 months ago complaining of "asthma." There was a history of a chronic cough which appeared after an attack of "the flu" two years prior to his first visit. The cough, though persistent and more troublesome at night than during the day, was in no way a manifestation of a debilitating illness. He had felt well during this time and had continued with his occupation. The cough, he stated, was productive of "clear mucus" and was never tinged with blood. He had taken his temperature sporadically and said that it was always normal or below normal. He had had no wheezing, dyspnea or pain in the chest. Three months before the onset of the cough he had consulted his dentist because of a sore mouth which was treated locally. The patient

* Received for publication June 1, 1948.

The work described in this paper was done under a contract with the Office of the Surgeon General, Department of the Army, Washington, D. C.

stated that it took about six months to improve the condition but that he was still troubled with soreness in the upper mouth which prevented him from wearing his "upper plate" continuously.

Six months after the onset of his cough and just 18 months before I first saw him he was awakened in the night, three hours after going to sleep, with shortness of breath, wheezing respirations and a sensation of tightness in his chest. These symptoms abated without medical assistance but recurred the following night at about the same time. After four such attacks had occurred on four consecutive nights he summoned a physician who made a diagnosis of bronchial asthma and who relieved his attack by giving him an injection of "adrenalin." Despite the elimination of his feather pillow and the empirical maintenance of a dust-free bedroom, he continued to have nocturnal attacks of asthma, though the severity of the attacks and their duration had been greatly ameliorated by the use at bedtime of an "aminophylline" rectal suppository and an "ephedrin" capsule.

Six months after the onset of his asthmatic symptoms he consulted an allergist. Numerous skin tests were made, all of which were said to have been negative. A roentgen-ray examination of the chest was said to have been "normal." The patient stated that a diagnosis of "intrinsic" asthma had been made, that he was given injections of a "vaccine," and that he had been instructed in the use of penicillin aerosol. After three months of such treatment, improvement was manifested by the fact that his attacks occurred only two or three times a week. But despite the continuation of his treatment, his attacks gradually became more frequent, and soon he began to have an attack now and then during the day. It was shortly thereafter that I first saw the patient.

During the entire illness the patient had never had symptoms of a rhinitis. There was no history of urticaria, eczema or migraine. There was no family history of allergy. The past history was irrelevant and remarkably void of illnesses, so much so that he was proud of the fact that prior to the onset of his present illness he had never sought the services of a physician.

Physical Examination: The patient was a well nourished man who did not appear ill. Though he coughed occasionally he was not short of breath. The temperature was 98.8° F.; the pulse was 90; the blood pressure was 132 mm. Hg systolic and 82 mm. diastolic, and the respirations were 20. The skin was of normal texture and without a blemish. The examination of the head was negative except for the mouth. Here and there over the portion of the gums covered by the upper denture were small white plaques. The mucous membrane about the plaques was fiery red. Several of the plaques were removed by scraping for direct microscopic examination and for culture. The lower teeth appeared to be in good condition, the tongue was quite clean, the tonsils had been well removed, and the oral pharynx was only slightly injected. There were no palpable glands in the neck or elsewhere. The trachea was in the midline and the thyroid was not enlarged. The right and left sides of the chest moved synchronously with deep inspiration. There were no deformities. Tactile fremitus was normal, and the percussion note was resonant everywhere. The bases descended 5 cm. on deep inspiration, and each Krönig's isthmus measured 5 cm. The breath sounds were normal in quality throughout, but they were diminished posteriorly over both lower lobes and there were musical râles to be heard everywhere. There were medium moist râles at both bases posteriorly. The remainder of the physical examination was quite normal.

Laboratory Examinations: The Kahn and Eagle serologic tests were negative. The hemoglobin was 15.0 gm.; the red blood cell count was 5.2 million, the white blood cell count was 7,850, the sedimentation rate (Wintrobe method) was 18 mm. (corrected), and the hematocrit was 47 mm. The differential leukocyte count was normal except for an eosinophilia of 16 per cent. The urinalysis was normal. The

direct microscopic examination of a plaque from the mouth revealed it to be composed entirely of hyphae and yeast cells. The unstained sputum contained many hyphae and yeast cells which were gram-positive. The sputum and scrapings from the mouth were cultured on Sabouraud's dextrose agar. After five days, creamy moist colonies developed in all tubes which displayed the cultural characteristics of *Candida albicans* as determined by subculturing on corn meal agar and into sugar fermentation tubes. *Staphylococcus aureus* and alpha hemolytic streptococcus were cultured from the sputum on bacteriologic media.

Intradermal skin tests with environmental, pollen and food antigens were negative. Skin tests with stock strains of bacterial vaccines gave delayed reactions of the tuberculin type to *Staphylococcus aureus* and *Staphylococcus albus* and to staphylococcus toxin. Skin tests performed with one protein and two carbohydrate fractions isolated from a concentrated *Candida albicans* broth filtrate gave interesting results. The one protein and the two carbohydrate fractions (the details of isolation will be reported elsewhere) gave large wheal reactions of the anaphylactic type after 15 minutes and also enormous reactions of the tuberculin type after 48 hours. The anaphylactic hypersensitivity was passively transferred to two recipients who previously had given negative immediate and delayed reactions to the *Candida albicans* antigens. Furthermore, 25 normal individuals were tested intracutaneously with the three different fractions and all individuals gave negative immediate reactions, but three gave small delayed reactions. Precipitin tests, in which each of the three fractions were used as antigens, were positive in a 1:16 dilution of the patient's serum.

The roentgen examination of the chest revealed peribronchial infiltration. No infection in the upper air passages was found, and roentgenograms of the sinuses were read as "clear."

A diagnosis of bronchial asthma and bronchitis due to *Candida albicans* was made and the patient was started on inhalations of sodium caprylate aerosol. A 10 per cent solution of sodium caprylate in propylene glycol was prepared and administered every three hours, so that the patient received from 1 to 2 gm. of sodium caprylate every 24 hours. The symptomatic treatment that he had been employing was not altered.

After two weeks of treatment the cough decreased in frequency and the sputum decreased in quantity. He continued to have mild attacks of asthma at night and occasionally during the day. After four weeks he was essentially free of asthma, and the examination of the chest revealed only an occasional musical r le. There was still a cough but the sputum was scanty. After six weeks the symptomatic therapy was discontinued. He remained free from asthma, the cough disappeared, and the examination of the lungs was negative. He continued to use sodium caprylate aerosol once daily for another four weeks before it was discontinued. The sputum cultures became negative for *Candida albicans* after four weeks of treatment. The lesions in the mouth disappeared after three weeks of treatment. It has been 14 months since treatment was discontinued and the patient has remained well and symptomless during this period.

COMMENT

This is the first case of bronchial asthma due to *Candida albicans* to be recorded in the medical literature. Furthermore, a new method of treating bronchitis due to *Candida albicans* has been introduced.

The patient had an oral infection due to *Candida albicans* which had preceded the onset of his respiratory symptoms by three months. Whether this infection, which was diagnosed as a denture sore mouth, represented the primary focus of infection is speculative; however, from the history it is reasonable to assume that

the infection spread from the mouth to the respiratory tract. The infection in the bronchi persisted for six months before manifestations of hypersensitivity in the form of asthma became clinically apparent. The patient demonstrated both the anaphylactic and the tuberculin types of hypersensitivity to the infecting organisms. The anaphylactic type of hypersensitivity was demonstrated by the large immediate skin reactions obtained from both the protein and the carbohydrate fractions isolated from the concentrated *Candida albicans* broth filtrate, and by the fact that such reactions could be passively transferred to two normal recipients. Delayed skin reactions, which were manifestations of the tuberculin type of hypersensitivity, were elicited to both the protein and carbohydrate fractions. These delayed reactions could not be passively transferred. Twenty-five normal control subjects failed to give positive skin reactions to the antigenic fractions.

Keeney, Ajello and Lankford¹ reported that sodium caprylate inhibited the growth of *Candida albicans* in vitro. Later, Keeney^{2,3} reported the effectiveness of sodium caprylate applied locally in the treatment of infections of the mucous membranes and skin due to *Candida albicans*. The patient described in this report afforded us the first opportunity to determine the effectiveness of sodium caprylate in the treatment of a bronchial infection due to *Candida albicans*. By clinical trial it was ascertained that a 10 per cent solution of sodium caprylate in propylene glycol could be administered without unpleasant side effects. A 15 and a 20 per cent solution proved irritating to the bronchial mucous membranes.

SUMMARY

A case of bronchitis and bronchial asthma due to *Candida albicans* and effectively treated with sodium caprylate aerosol has been reported.

BIBLIOGRAPHY

1. Keeney, E. L., Ajello, L., and Lankford, E.: Studies on common pathogenic fungi and on *Actinomyces bovis*. I. In vitro effect of fatty acids, Bull. Johns Hopkins Hosp. 75: 377, 1944.
2. Keeney, E. L.: Medical mycology, M. Clin. North America, March 1945. Nationwide Number, pp. 323-342.
3. Keeney, E. L.: Sodium caprylate. A new and effective treatment for moniliasis of the skin and mucous membranes, Bull. Johns Hopkins Hosp. 78: 33, 1946.

GENERALIZED SCLEREDEMA: REPORT WITH AUTOPSY FINDINGS *

By IRVING LEINWAND, M.D., New York, N. Y.

SINCE Buschke¹ in 1900 described the syndrome designated as scleredema adultorum there have been 99 cases reported in the literature collected and reviewed by Vallee,² to which he added four. One autopsied case had been reported by Stenbeck³ (1940), in which he noted visceral lesions resembling those found in the skin. In view of the overwhelming preponderance of recoveries

* Received for publication April 22, 1948.

in this disease, some doubts have been expressed as to the diagnosis of a true scleredema in that case: although the clinical picture resembled scleredema, a review of the pathologic report suggests a diagnosis of scleroderma.

The systemic nature of scleredema has been recently proposed by Vallee.² That the skin was not the only system affected has been noted by Voss,⁴ O'Leary⁵ and Schnitzer,⁶ whose patients had hydrarthroses. The purpose of this report is to reaffirm the systemic nature of this disease and to present the confirmatory evidence of the autopsy findings. The patient was first seen by this author only eight months after the onset of her disease, and was observed by him and others until her death some six years later.

CASE REPORT

The patient was admitted to the New York Post Graduate Medical School and Hospital on January 4, 1942, with a history of progressive stiffening of the skin for 10 months. The stiffening of the skin of the neck, which had begun 10 months before, was followed by a similar process on the back, shoulders, breasts, upper arms, and front of the neck. Her face became involved about four months after the onset of the process. Cold greatly aggravated her disease. The stiffness was accompanied by pain on motion, because the patient was "skin bound." The remainder of her body was not involved. She had occasional trouble in swallowing because of the stiffness of the skin of her neck. She had had severe hot flashes for several years following a complete hysterectomy in 1925. No other menopausal manifestations were present. She had been receiving thyroid, 0.5 grain, for a tired, run down feeling. She had lost 10 pounds while taking thyroid, but had regained five pounds in the past two weeks without thyroid.

Her general health had been good. There was no preceding acute infection and no history of any allergies. She had had an appendectomy in 1916, a hysterectomy in 1925 and a tonsillectomy in 1929. She had fallen into the cellar of her house and injured her right arm. Roentgen-ray showed that the humerus had been previously fractured and healed. There were no eye, ear, nose, throat, respiratory or cardiac complaints. The appetite was good, but digestion was poor with carbohydrate meals. She was very constipated and took two cathartic pills every day. She had hemorrhoids without any symptoms. No nausea or vomiting was present, except that voluntarily produced with fingers when she had too much gas. There were no genito-urinary complaints and no neurologic symptoms.

The patient had been born in Germany, had moved to the United States, and had never lived in the tropics. She was married, and her husband and two children were well. She slept poorly, drank two cups of tea, one cup of coffee. She did not smoke, but drank an occasional beer or highball. The diet was adequate but lacked vitamin C. She was a very active housewife. Her father had died in old age; her mother was living and well. Eleven siblings were all well. There were no familial diseases.

Physical examination revealed a well developed 58 year old woman in distress. Weight, 170 pounds; temperature, 98.6 F. The skin was stiffened over the face, neck, shoulders and arms down to elbow and back, and abdomen down to umbilicus. The skin of the breasts was soft, but the medullary tissue of the breast was of leathery consistency.

Head: Eyes: Muscle movements normal; pupils are equal and react to light and accommodation. *Fundi:* Vessels and discs are normal. Ears and nose clear, pharynx clear, tissues pallid, tongue moist, teeth in fair repair. *Neck:* Thyroid not palpable; trachea in midline; no glandular enlargement. *Thorax* and spine are symmetrical; no tenderness; no skeletal defects. *Lungs:* Clear to percussion and auscultation. *Heart:*

Regular sinus rhythm, not enlarged; P_2 rough; no murmurs. Pulse rate equals ventricular rate of 60. *Blood pressure*: Right arm 110/76 mm. Hg, left arm 110/80; right leg 136/94, left leg 156/94. *Abdomen*: No tenderness present. Liver, spleen and kidney not palpable. *Rectal and pelvic*: Negative. *Extremities*: The feet are very warm without rubor. Pulsations in both dorsalis pedis arteries are easily palpable. *Reflexes*: Upper, deep—equal and active. Lower, deep—equal and hyperactive. No Babinski or Hoffman sign is present.

Basal metabolism: January 7, 1942 minus 7 (efficiency of circulation calculated at 102 per cent). *Steroid metabolism*: 637 c.c. urine voided in 24 hours, 9.9 mg. 17-ketosteroids in 24 hours. Normal range 5.1 to 14.2 mg. in 24 hours (average 9.0 mg.). *Blood chemistry* (December 19, 1941): Urea nitrogen 18.5; non-protein-nitrogen 42.0; ratio 44 per cent; chlorides 505 mg. per cent; sugar (true glucose) 100; inorganic phosphate 3.3 mg. per cent; calcium 9.8 mg. per cent; phosphatase activity 3.1 units; cholesterol (total) 250 mg. per cent, esters 140 mg. per cent, esters (total) 56 per cent.

Urea clearance test (December 19, 1941): First hour—99 per cent of average normal; second hour—99.8 per cent of average normal (corrected for surface area). *Serum protein* (January 9, 1942): Total 7.9 gm. per cent. Albumin 3.5 gm. Globulin 4.4 gm. Ratio 0.8.

Vitamin C saturation test (December 22, 1941): 1.5 hours 67.7 mg. per 150 c.c.; 3.5 hours 31.6 mg. per 325 c.c.; 5 hours 99.3 mg. per 475 c.c. Saturation index 115 mg./24 hours (normal above 450 mg.).

Electroencephalogram (January 8, 1942). *Impression*: The pattern is suggestive of some mild electrophysiologic disturbance of the cortex, particularly over the posterior parietal and occipital regions bilaterally. The character of the pattern cannot be correlated with any definite clinical syndrome, so far as is known at the present time. A repeat is suggested at some future date.

Electrocardiogram (January 6, 1942). $S_{2,3}$, low T_4 , left axis deviation. *Impression*—within normal limits.

Biopsy (January 9, 1942). Skin, muscle, and fascia from left trapezius area. *Gross*: Specimen consists of a portion of skin measuring 1.5 by 1.3 cm. with wedge-shaped subcutaneous tissue attached. The dermis is apparently thickened and sclerotic and in one portion measures 0.4 cm. *Microscopic*: The epidermis is thin and, in places, rete pegs are absent. The collagen of the uppermost papillary layer shows a moderate degree of granularity. The deeper bundles of collagen of the dermis appear thickened and hyalinized and are in many places separated by clear spaces which contain no granular precipitate. The stain for elastic tissue indicates a slight reduction in elastic fibers. The sebaceous glands are not remarkable. The sweat glands are slightly atrophic. A sprinkling of histiocytes is found about several of the arterioles in the upper dermis. No fibrinoid necrosis such as is seen in disseminated lupus erythematosus is found here. No significant basophilia of the collagen is apparent. A small fragment of skeletal muscle is included which shows no significant change. The changes reach the resected edges.

Diagnosis: Piece of skin compatible with that seen in scleredema.

The patient was given no treatment other than a high vitamin, high caloric diet, and was advised that the prognosis was guarded but that a spontaneous remission could probably be expected, although the time was indefinite.

I was not able to see this patient during the war years. In September, 1942, the patient was seen at the Mayo Clinic by Dr. Paul O'Leary,⁷ who confirmed the clinical diagnosis of scleredema. A skin biopsy taken from the area of the left breast at that time was reported by Dr. H. Montgomery⁷ as being that of scleredema. She remained there about a month, during which time she had some fever treatments with the hypertherm machine in addition to some physical therapy. Between November,

1942, and June, 1944, when she again reported to the Mayo Clinic, she had had some roentgen-ray therapy. At the Mayo Clinic in 1944 she was given some typhoid injections from which she had only a moderate reaction. She also had several treatments with the hypertherm machine which she seemed to think made her more comfortable. She complained of some difficulty in swallowing, but roentgenograms of the stomach and esophagus were negative.

From the laboratory standpoint, urine examinations were negative. There was a mild anemia, as evidenced by a hemoglobin of 11.6 gm. per cent, 3.91 million erythrocytes, and 8,800 leukocytes. The Wassermann test was negative. Roentgen-ray of the chest in September, 1942, and again in June, 1944, was negative. Roentgen-ray of the colon was negative. Roentgen-ray of both feet showed some hypertrophic changes in addition to bilateral bunions, which were operated on. The basal metabolic rate in September, 1942, was minus 5 per cent and in June, 1944, was plus 1 per cent. Sedimentation rate at the same intervals was 49 and 67 mm. per hour by the Westergren method.

During 1945 the patient spent the winter in Florida, where she was a little more comfortable. Her condition apparently grew slowly but progressively worse so that in the summer of 1946 she began to have some exertional dyspnea. By winter this had become severe and the patient sought local medical care. Her condition eventually became so precarious that it was thought advisable to return her to the North.

The patient was admitted to the St. Clare's Hospital in acute distress after an eight hour plane flight on February 19, 1947. Her chief complaints were difficulty in breathing, pain in the back, cough and fever for the past three weeks. The patient stated that for the past three months she had difficulty in breathing on slight exertion. During the past three weeks she had had a bad cough and had been confined to bed during treatment for "a cold." The patient stated that she could not eat large amounts of food at one sitting because of inability of the abdomen to expand. She attributed some of her difficulty in breathing to the same cause. It was agony for her to sit up because of extreme pain in both sides of the lower back, although she felt more comfortable sitting up as far as her breathing was concerned. Her difficulty in breathing had become worse; her pain, cough and all her symptoms had become more pronounced. Her past history was previously recorded.

Physical examination revealed a middle aged, white female, well developed, in acute distress. *Eyes, Ears, Nose and Throat:* Unchanged. *Lungs:* Moist râles were audible throughout both lungs posteriorly, more pronounced at the bases. *Heart:* A systolic murmur was heard over the entire precordium. There was regular sinus rhythm. The pulse was 104. The heart sounds were muffled. Blood pressure was 120/80. *Abdomen:* There was difficulty in palpation due to the thickening of the skin and slight distention of the colon. However, it was thought that the liver was probably three fingerbreadths below the costal margin. *Extremities:* There was 1 plus non-pitting edema of both legs. *Skin:* The entire body appeared to be sheathed in a plastic rubber replica of the skin. The portions least involved were the hands and feet. The skin was a pale yellow color, almost a light lemon. It could not be creased in folds. Although its consistency gave one the impression that pressure would produce pitting, this was not the case. The skin appeared definitely thickened with loss of elasticity.

Course: The patient was digitalized by the two dose administration of 1.2 mg. of digitoxin. This was followed by 0.4 mg. every six hours until the pulse approached normal, at which time 0.2 mg. was given daily as a maintenance dose. Oxygen was administered by nasal catheter. Penicillin G sodium 50,000 units in normal saline was administered every three hours until 24 hours after the temperature had returned to normal. Vitamin C was given in one gram dose daily for five days, in addition to vitamin B complex given parenterally. Six transfusions of 500 c.c. each of whole

blood were given during the next eight days. Administration was by the citrate drip method, about 40 to 60 drops per minute. On admission (February 19, 1947) examination of the blood revealed hemoglobin 6.5 gm., red blood cells 2.04 million, and white blood cells 8,400. On February 25, 1947, the hemoglobin was 9.0 gm., red blood cells 3.40 million, and white cells 9,700. On February 27, 1947, the hemoglobin was 11.5 gm., red blood cells 3.94 million, and white blood cells 14,200. The urine on admission had a specific gravity of 1.011, with a trace of protein. Three days later the specific gravity was 1.017, with no abnormal findings present. Roentgen-ray examination of the heart and lungs revealed the heart to be enlarged in all diameters. There was some density about the hilar area extending to the bases of both lungs. The impression was that of an enlarged heart, with findings in the lungs consistent with that seen in cardiac decompensation. The day before death (February 27, 1947) the blood urea nitrogen was 37.2 mg. per cent, the non-protein-nitrogen was 55 mg. per cent, and the creatinine 1.6 mg. per cent. An electrocardiogram taken after digitalization showed normal rate, rhythm and conduction, with left axis deviation and low voltage of all T waves. The RST segment was depressed in Leads I and CF, T₁ inverted, T₂ low and variable, T of a₁ inverted.

Her course in the hospital was progressively downward in spite of all treatment. The temperature dropped to normal within 48 hours after the institution of penicillin therapy, which was kept up for five days. It was thought that the cardiac failure was in great part due to the marked anemia, since the patient did not respond to digitalization. Even with a blood picture approaching normal there was no response. She complained bitterly of pain in her back, which was only partially relieved with opiates. On the seventh day she became irrational. There were moist râles present throughout both lungs. There was marked dyspnea. She became comatose and died nine days after admission.

An autopsy was performed two hours after death. *Clinical diagnosis:* (1) Generalized scleredema; (2) Bilateral bronchopneumonia; (3) Cardiac failure; (4) Renal failure. *Pathologic diagnosis:* (1) Systemic scleredema; (2) Confluent lobular pneumonia; (3) Pulmonary edema; (4) Bilateral hydrothorax; (5) Hydropericardium; (6) Atherosclerosis of the aorta; (7) Arteriosclerosis of small pulmonary arteries; (8) Passive congestion of liver and spleen; (9) Schimmelbusch's disease of the breast.

Postmortem Findings: * *General:* The body is that of a white female, aged 58 years. Development is within normal limits. The nutritional status is fair. The skin over the entire body is brawny, tense, and turgid to the touch. It is pale white in color except over the forearms and legs, where there is a pale lemon tint to the skin. Rigor mortis is absent. There is a blotchy lividity over the face, neck and dependent portions posteriorly. The hair is gray. The pupils are wide and equal. The eyes are blue. The sclerae are white. There is no palpable lymphadenopathy. There are three scars on the anterior surface of the body. One scar is on the chest and is to the left of the midline. It is old, well healed and measures 4 cm. in length. The other two scars are on the abdomen. Both are old and well healed. One is suprapubic and midline in position. It measures 12 cm. in length. The other scar is oblique and is located in the right lower quadrant. It also measures 12 cm. in length. The joints are all freely movable. The abdomen is moderately protuberant.

Primary Incision: The body is opened by a "Y" incision. The skin is thickened and rigid and shows a loss of normal elasticity. The subcutaneous fat is large in amount and bright yellow in color. The recti muscles are somewhat thin and show areas of fat replacement between muscle fibers. There is a very small amount of clear yellow fluid in the abdomen. The intestines are all moderately distended. There are some old adhesions of the omentum to the anterior abdominal wall at the site of

*The autopsy was performed and reported by Dr. Joseph Mendeloff.

the previous operations. The abdominal viscera are all normal in position. On opening the chest there is an increased amount of fat in the mediastinum. The left pleural space contains about 50 c.c. of clear pale amber fluid. The right pleural space contains about 300 c.c. of clear pale amber fluid.

The left lung is partially bound down to the chest posteriorly and laterally by dense bands of easily separable adhesions. The pericardium contains 200 c.c. of clear pale amber fluid.

In the neck the various structures are densely adherent to each other and are embedded in connective tissue and fat. There is considerable difficulty in reflecting the skin.

The thyroids are normal in size and position. On section, they are composed of irregular lobules of pale brown granular tissue. The parathyroids are inconspicuous. Four small fragments are removed for histologic identification. The larynx is patent and shows no intrinsic abnormalities. The diaphragm is thin.

Lungs: The left lung weighs 430 gm. Both parietal and visceral pleurae are shiny. The lung is crepitant and soggy. On section, both lobes show a mottled pinkish-gray surface. A thin watery fluid exudes from the cut surface. In the lower and posterior portions of the lower lobe there are small scattered areas of solid granular parenchyma. There are no significant abnormalities of the bronchi or pulmonary vessels of the left lung. The bronchial nodes are small, soft and black.

The right lung weighs 450 gm. Parts of the posterior and lateral pleura are shaggy. All three lobes are crepitant and soggy. On section, the cut surfaces of the upper and middle lobes present mottled pinkish-gray surfaces which are similar to the opposite lung. In the lower lobe there are small, irregular, solid red granular areas similar to those found in the opposite lung. The bronchi and pulmonary vessels of the right lung show no significant abnormalities. The bronchial lymph nodes are small, soft and black.

The trachea shows no significant gross abnormalities.

Heart: The heart weighs 250 gm. There is a small amount of subendocardial fat. On opening the heart, the endocardium is for the most part translucent, there being only a few small scattered opaque areas. There are no significant abnormalities of the valvular leaflets. The orifices of the valves are all within normal limits in size. The leaflets of the mitral valve show a few small thin areas of gray opacity. The walls of the ventricles have a rubbery rigidity. On section, the myocardium is pale red in color. Both auricular appendages are empty. Both coronary orifices are narrowed by surrounding pale white atheromatous deposits. There is a transverse white intimal ridge above the coronary orifice. All coronary arteries are patent throughout their entire courses. The walls are thin, soft and pale yellow in color.

Aorta and Vessels: The aorta is elastic and pale yellow in color. There are a few scattered, very small, darker yellow atheromatous deposits. All arterial orifices are surrounded by small elevated white intimal atheromatous deposits, but there is no narrowing of the orifices. The pulmonary artery opened in situ contains free blood.

Spleen: The spleen weighs 220 gm. There are some adhesions of the capsule to surrounding structures. The capsule is wrinkled, opaque and blue-gray in color. On section, the parenchyma presents a rubbery consistency. The cut edges remain rigid. The surface is deep red and diffusely mottled by tiny prominent gray areas. The cut surface has a glazed appearance.

Liver: The liver weighs 2,190 gm. The capsule is smooth and translucent. The edges are slightly rounded. On cut section, the parenchyma discloses a rubbery consistency. The cut edges remain rigid. For the most part the parenchyma is yellow. There are, however, scattered peripheral areas where the parenchyma shows extreme congestion and presents a nutmeg appearance.

The wall of the gall bladder is thin. The external surface is smooth. The mucosal pattern is finely granular. It contains a small amount of thick dark green viscid bile. The extrinsic biliary pathways are patent.

Pancreas: The pancreas is normal in size, shape and position. On section, the parenchyma is firm and presents a lobular architecture composed of mottled brown parenchyma. The pancreatic ducts are patent.

Adrenals: Both adrenals are normal in size, shape and position. They are somewhat friable. On section, the cortices are deep brown in color. The medullary markings are indistinct.

Gastrointestinal Tract: There are no significant intrinsic or extrinsic abnormalities of the esophagus, stomach, small intestine, colon or rectum. The appendix is absent (surgical removal). In the colon there is a small amount of semi-solid black material.

Genito-Urinary Tract: The left kidney weighs 210 gm. The capsule strips easily, leaving a smooth deep red surface which still shows remains of fetal lobulations. On section, the cortical and medullary markings are accentuated by a deep red congestion. The parenchyma has a rubbery consistency and presents a glazed surface. The cut edges are rigid. The ratio between the cortex and medulla is within normal limits. There is a marked increase in peripelvic fat. The mucosa of the pelvis is markedly congested. There are no significant abnormalities of the left ureter.

The right kidney weighs 260 gm. It is similar in gross appearance to the opposite kidney.

Bladder: The bladder is moderately distended and contains a pale amber urine. The wall is thin. Mucosal markings are within normal limits. The surface shows slight congestion.

Internal Genitalia: The uterus, cervix and tubes are absent. On each side of the lateral wall of the pelvis there are small globular masses measuring 3.5 cm. in diameter. They consist of a soft, spongy and slightly cystic tissue which resembles ovarian stroma.

Bone Marrow: The bone marrow of the vertebral column and ribs is plentiful in amount and pale red in color.

Lymphatics: There are several small abdominal peri-aortic nodes just above the bifurcation of the aorta. These vary in size from 1 to 1.5 cm. They are soft and succulent. The cut surfaces are brown. No other prominent lymph nodes are noted.

Brain: Not examined.

Microscopic Findings: Heart: The muscle cells and nuclei show no significant changes. There is some widening of the spaces both between small muscle bundles and large groups of muscle bundles. There are small and moderate amounts of both loose and dense connective tissue about myocardial arteries. Some of the myocardial arteries show thickening of their walls. In some areas of the pericardial fat there are a few sparse collections of lymphocytes. A section of the base of the mitral valve does not show any significant changes. There is slight thickening of the sub-endocardial connective tissue of the auricle.

Aorta: There is some hyalinization of the subendothelial aortic connective tissue.

Peri-Aortic Lymph Node: The architecture is altered, and numerous vascular channels are widely dilated and filled with coagulum. Follicles are inconspicuous. The lymphoid tissue is divided into small lobules and nests which are separated by connective tissue trabeculae of varying widths. The lymphoid tissue consists of small and medium sized lymphocytes which are loosely arranged. An occasional remainder of a follicle reveals small numbers of pyknotic cells. There are small numbers of plasma cells and rare eosinophils. In the surrounding fat between the fat cells there are small collections of pale, basophilic and eosinophilic homogenous material.

Lungs: Scattered groups of pulmonary alveoli are filled with erythrocytes, polymorphs, and occasional mononuclears and histiocytes. There is a small amount of

eosinophilic material. In both intermingled and closely adjacent acini there is a small amount of pink coagulum. Other groups of pulmonary alveoli are delicate. There is some congestion of the septal capillaries.

Bronchus: There are a few small focal collections beneath the surface epithelium. An adjacent peribronchial node shows changes similar to those described in the periaortic nodes. In addition, there are large numbers of macrophages filled with granular brown pigment. There are also smaller numbers of macrophages filled with a golden brown pigment. A few branches of the peribronchial arteries show calcification of the media.

Liver: The architectural pattern of the liver is well preserved. Central veins are moderately dilated. In some areas there is congestion of the sinusoids. The liver cells show a granular eosinophilic cytoplasm.

Gall Bladder: There are no significant changes of the mucosa or muscularis. The serosa contains a moderate amount of fat and between the fat cells there are small deposits of pale pink coagulum.

Esophagus: There are no significant histologic changes.

Stomach: In the fat of the submucosa there are small interstitial deposits of a pink coagulum. There are no other significant histologic abnormalities.

Small Intestine: In the mucosa there are large numbers of macrophages which contain a coarse brown granular pigment. There is some edema of the mucosa. In the submucosa there is a large amount of pink coagulum.

Colon: In the mucosa there are small, sparsely distributed numbers of oval cells which contain a coarse granular brown pigment. There is some edema of the mucosa.

Omentum: A lymph node in the omentum shows dilatation of vascular channels. These are filled with pink coagulum. No clear-cut lymphoid follicles are distinguishable. The lymphocytes are loosely arranged. In the surrounding fat there are small amounts of intercellular pink coagulum.

Spleen: The lymphoid follicles are small. There are scattered patchy areas of congestion of the red pulp. The cords of Billroth appear slightly thickened due to a cellular hyperplasia. There appears to be some proliferation of the reticular endothelial cells. In some areas the sinusoids are quite distinct and the lining cells are prominent.

Pancreas: There are no significant changes of the islets of Langerhans. There are no significant changes of the acini.

Kidney: The glomerular tufts are moderately congested and the spaces are somewhat dilated. Within some of the spaces there is some eosinophilic debris. The tubular epithelium shows cytoplasmic fragmentation. The cytoplasm is granular and eosinophilic. Nuclei are fairly well preserved. Interlobular arteries show some thickening of their walls. There are small collections of lymphocytes beneath the pelvic mucosa.

Urinary Bladder: There are no significant histologic changes.

Ovary: The stroma is densely fibrocellular. It contains numerous corpora albicantia. There are a few tiny cysts near the periphery, lined by an epithelium and containing a basophilic coagulum in their lumina. Some areas of the ovary are densely hyalinized. There is moderate vascular congestion.

Breast: The stroma of the breast consists of patchy areas of adipose tissue and dense hyalinized connective tissue. Scattered throughout are numerous lobules of terminal ducts. These are rather prominent. Some ducts show evidence of epithelial proliferation. There are also groups of large dilated ducts and these are filled with sheets of epithelial cells in which there are tiny spaces. These epithelial cells are uniform in appearance.

Thyroid: Thyroid acini are fairly uniform in size and shape. A few small lobules contain large acini. They are filled with a pink colloid and are lined by single layers

of flattened epithelium. There are a few areas in the thyroid where the interacinar connective tissue is hyalinized and causes some compression and atrophy of the thyroid acini. The cytoplasm is vacuolated. Thyroid shows involution changes.

Parathyroids: No significant histologic changes.

Adrenals: There is moderate sinusoidal congestion. The cytoplasm of the cortical cells is granular and vacuolated. There are no significant changes in the medulla.

Skin of the Chest Wall: There is a marked reduction in the thickness of the corium. The rete pegs are absent in some areas and are small in others. The connective tissue of the papillary bodies is eosinophilic and granular. There are a few small scattered lymphocytes. In the deeper layers of the corium the connective tissue is arranged in irregularly formed collagen bundles which are clearly separated from each other. In the fat of the subcutaneum there are small amounts of intercellular basophilic material.

Skin of the Abdomen: The changes are similar to those described for the skin of the chest. In some areas the corium is extremely thin and atrophic.

Rectus Muscle: Muscle bundles are reduced in number and are separated by lobules of adipose tissue. In the latter, there are moderate amounts of intercellular pale staining eosinophilic material.

Pectoral Muscle: Fatty tissue between muscle bundles is less in amount. However, muscle bundles are still separated by both fatty tissue and small amounts of pink staining coagulum.

Soft Tissues of the Neck: The soft tissue of the neck consists of large amounts of adipose tissue and small amounts of connective tissue. Particularly in the former there are small amounts of intercellular pink and basophilic coagulum.

Parietal Pericardium and Surrounding Fat: The parietal pericardium consists of dense connective tissue. In the surrounding fat there are a few small amounts of intercellular coagulum. In the surrounding small groups of blood vessels there are closely packed collections of lymphocytes.

Ribs: The marrow is densely cellular, and cells of both the erythrocytic and granular series are well represented. Hematopoiesis appears to be active. There are occasional megakaryocytes. The bony trabeculae show no significant changes.

DISCUSSION

Clinical Manifestations: The clinical picture of this disease has been adequately reviewed and described in previous reports. The distribution and progression of the skin lesion were characteristic. The neck has been described in the literature as the most frequent site of the initial process. In this patient the tissues of the neck were so adherent to each other that they could scarcely be separated at autopsy. Of the entire body only the hands and feet remained uninvolved. The skin changes as described in the examination were typical. The waxy feeling of the skin is unmistakable: it feels just as the skin does in a paraffin bath. The extreme pain present in this patient has not been reported as a constant finding in this disease. Attempts at vasodilatation by the use of various fever-producing agents seem to have afforded the patient some symptomatic relief, although they apparently have no relation to remission or cure. This patient felt better with these measures and went to a warmer climate because of the relief she experienced from them. The laboratory findings up until the terminal phase were within normal limits, except for the increase in serum globulin. This is in agreement with those findings reported in other cases. It is interesting to note the increase in serum globulin, which I believe is a not uncommon finding in diseases of the

collagen system. The electrocardiogram in January, 1942, showed minor changes which were within normal limits. The electrocardiogram taken the week before death after the patient had been digitalized, showed many changes associated with digitalization. However, the low voltage can certainly be attributed to the edema.

Etiology: It has been the general opinion that the majority of cases with scleredema give a history of an antecedent acute infection. This was even considered a point in favor of the diagnosis. However, this was not true of all patients reported, nor was it true in this particular case. It should be noted that the absence of any inflammatory reaction in this disease would favor a metabolic disturbance rather than an infection. It may be, however, that a specific infection precipitates such a disturbance in a susceptible individual. Selye,^{8,9} in determining the effect of folliculoid hormones applied to abnormal skin, speculates on the possibility that the steroids or the folliculoids may be in some manner responsible for the disease. He produced a lesion in the hairless mouse morphologically similar to the cutaneous changes typical of scleredema adutorum.

Fish¹⁰ in 1930 reported a case of scleroderma associated with juvenile rheumatism. This was a report on a 13 year old female with an attack of rheumatic fever which was followed in three weeks by stiffness and swelling of the skin of the arms and face. Later the trunk and legs were involved. Physical findings were consistent with a diagnosis of rheumatic fever. No biopsy was done. The skin condition began to improve and continued to improve during the follow-up period. This case would appear to be one of scleredema rather than scleroderma from a standpoint of history, distribution of the lesion, and course. I mention this case because of the apparently small number of cases of scleredema reported and because of the rheumatic history in this particular case. Epstein¹¹ had one patient with a similar history. It should be pointed out also that there have probably been other cases of scleredema reported as scleroderma, and vice versa. It is interesting to note also that this disease occurs predominantly in females, as do all of the other diseases involving the collagen system or connective tissue system.

Course: It is agreed that the prognosis as regards life is generally good. Except for Stenbeck's case, all other cases reported had spontaneous remissions after varying intervals of time. It is possible that there have been other fatal cases that have been improperly diagnosed.

Diagnosis: Scleredema must be differentiated from scleroderma and dermatomyositis, which it closely resembles in the acute phase. In scleredema the hands and feet are never affected. There is no pigmentation or calcinosis in the skin. There is no atrophy of the muscle. The skin itself is not atrophied. Raynaud's syndrome is usually absent. Pathologically in scleredema the epidermis is not affected. The process is in the deeper portion of the skin and subcutaneous tissue. There is no inflammatory reaction or endarteritis.

In scleroderma the superficial skin layers are frequently involved and there is usually a cellular reaction about or involving the blood vessels. There is a sclerosis of the underlying tissue so that the tissue is thick and hard. The hands are always involved in generalized scleroderma. There is frequently bronze pigmentation of the skin. Calcinosis occurs in some cases. Atrophy of the underlying muscle is common.

Dermatomyositis may offer some differential problem. This disease is usually progressive and more prostrating. Erythematous skin lesions may be present. Weakness, muscle pain, atrophy and fever are usually prominent.

Myxedema should offer little problem. The basal metabolic rate is below normal, the blood cholesterol is elevated. The skin is coarse and dry rather than waxy. A therapeutic response to thyroid is rapid. Any other type of edema can be ruled out by the presence of other signs of the disease, such as cardiac decompensation, renal failure, etc.

Nature of the Disease: In the cases in the literature in which the complaints of the patient were carefully noted, many symptoms referable to visceral involvement are found. For example, in the series of 15 cases reported from the Mayo Clinic by O'Leary and his associates⁸ it is interesting to note that in cases 7, 9, 14 and 15 there were symptoms referable to the viscera. Dysphagia was apparently the most common symptom. Swelling of the tongue and pharynx have been reported.^{11, 12, 13} Two of the four cases reported by Vallee had hydrothorax; one had pericardial effusion. Apparently these were systemic lesions which appeared concurrently with the skin lesions and disappeared or subsided with the involution of the surface lesions. Epstein, in discussing the paper of Sweitzer and Laymon,¹⁴ states that "the pathological picture shows why the skin heals without any serious damage. There is little inflammatory reaction. The disease consists simply of an increase in size of the collagen bundles and the deposit of a mucin-like material in the tissue. There is no endarteritis."

I believe that such is the case in the viscera as well as in the skin. That this is more than mere speculation is shown by the fact that, in the reported cases with remission or involution of the skin lesions, any symptoms referable to systems other than the skin also disappeared. The effusions noted in Vallee's cases disappeared with remission of the skin lesion. When one reviews the autopsy findings in the case here reported, one is impressed by the diffuse distribution of the edema and the absence of any other striking pathology. The gross examination revealed effusions in the pleural, pericardial, and peritoneal cavities. Edema and a peculiar rubbery consistency of many of the viscera sufficient to hold the tissues rigid after section were noted. There also appeared to be some areas of fat replacement between the muscle fibers of portions of the skeletal muscles. The findings otherwise were not remarkable. Microscopic examination revealed swelling of the collagen, with separation of the bundles resulting in clear spaces. These could easily be mistaken for artefacts reproduced in cutting sections. The absence of an inflammatory reaction only serves to further this impression. In many sections there were deposits of some intercellular substance in the fat which stained either acid or base. There is no doubt that, with the method of fixing the tissue, most of the intercellular material which has previously been noted in other reports was lost. Not enough is known of the histochemical nature of this material. It is unfortunate that we were not prepared to make such stains as would contribute more information regarding the nature of this material. After examining all these sections one is uncertain as to the exact cause of death. Should the pathologist be given a series of such slides without consideration of a clinical diagnosis, it would be difficult to give an opinion on the sections alone.* The microscopic picture in the viscera is the same as seen in the skin. The edema present is sufficient to interfere with the normal function of the affected tissue. This is readily apparent in the skin. If the same pathologic change attacks the viscera, then a similar condition may be visualized.

* Dr. Paul Klemperer, pathologist of the Mt. Sinai Hospital, was kind enough to review the pathologic sections.

The pathologic changes in scleredema consist chiefly of thickening and hyalinization of the collagen bundles with the production or deposition of a mucin-like material between the fibers. Since these changes occur throughout the body, it would seem logical to include this disease among those known as diseases of the collagen system. This is particularly applicable when one considers the fact that the pathogenesis of disease of the collagen system is probably concerned mainly with the intercellular substance.¹⁵

The case reported by Stenbeck showed a process in the skin which began in the face and eventually spread to the neck. This could have been diagnosed clinically as scleredema. This is not true of the postmortem findings. In the description of the gross findings, gray-white dense fibrous connective tissue infiltration was found practically everywhere, particularly in relation to the gastrointestinal tract. Intestinal obstruction has been produced in this manner in at least four cases of scleroderma,^{16, 17, 18} just as in the case reported by Stenbeck. Moreover, in the report of the microscopic examination a fibrinoid degeneration of the collagen is described. Fibrinoid degeneration does not occur in scleredema. It does occur in scleroderma.

Touraine, Gole and Soulignac¹⁹ have grouped scleredema, dermatomyositis and scleroderma under the general classification of "La cellulite sclerodermiforme extensive bénigne." I think that these diseases are far from benign but that they are closely associated, differing chiefly in the extent of the damage and the portions of the system affected. O'Leary has repeatedly stressed the difficulty of differentiating these three diseases in the early stages. Later in the disease, scleroderma may be easily distinguished but dermatomyositis may still offer difficulty.

The three conditions should, however, be distinguished in that the course and certainly the final disposition are not the same in all three of them.

SUMMARY

1. A fatal case of scleredema adultorum is presented.
2. The pathologic picture in the viscera is comparable to the changes in the skin.
3. Confirmatory findings at necropsy emphasize the generalized nature of the disease.
4. The absence of inflammatory changes permits a remission of the systemic lesions just as it does in the skin.
5. It is suggested that scleredema is truly another of the diseases of the collagen system.

BIBLIOGRAPHY

1. Buschke, A.: Vorstellung eines Falles von Skleroedem vor der Berliner Gesellschaft für Dermatologie, Arch. f. Dermat. u. Syph. 53: 383, 1900.
2. Vallee, B. L.: Scleredema: a systemic disease, New England J. Med. 235: 207-213, 1946.
3. Stenbeck, A.: Ueber einen Fall von Skleroedem mit Augenveränderungen, Acta ophth. 18: 76-84, 1940.
4. Voss: Skleroedema adultorum Buschke, Zentralbl. f. Haut- u. Geschlechtskr. 59: 248, 1938.
5. O'Leary, P. A., Waisman, M., and Harrison, M. W.: Scleredema adultorum, Am. J. M. Sc. 199: 458-466, 1940.

6. Schnitzer, A.: Ueber zwei Fälle von Sklerodema adultorum, *Dermatologica* 84: 215-224, 1941.
7. Personal communication.
8. Selye, H.: Effect of Estradiol locally applied to abnormal skin, *Arch. Dermat. and Syph.* 48: 188-192, 1943.
9. Selye, H.: Effect of folliculoid hormones and abnormal skin, *Arch. Dermat. and Syph.* 50: 261-263, 1944.
10. Fish, H.: Scleroderma associated with juvenile rheumatism, London County Council, Ann. Report 1930-32, vol. 4, pt. 3, p. 10.
11. Epstein, N. N.: Scleredema adultorum (Buschke) *J. A. M. A.* 99: 820-826, 1932.
12. Wiener: Sklerodem und Zungenveränderung im Verlaufe eines Falles von perniziöser Anämie, *Zentralbl. f. Haut- u. Geschlechtskr.* 17: 268, 1925.
13. Frank, L. J.: Scleredema adultorum (Buschke): report of case involving tongue, *Arch. Dermat. and Syph.* 36: 1052, 1937.
14. Sweitzer, S. E., and Laymon, C. W.: Scleredema adultorum (Buschke), *Arch. Dermat. and Syph.* 37: 420-430, 1938.
15. Klemperer, P.: Diseases of the collagen system, *New York Acad. Med.* 10: 581-588 (October) 1947.
16. Bevans, M.: Pathology with special reference to changes in the gastrointestinal tract, *Am. J. Path.* 21: 25 (Jan.) 1945.
17. Goetz, R. H.: The pathology of progressive systemic sclerosis (generalized scleroderma), *Clin. Proc.* 4: 337-392 (Aug.) 1945.
18. Leinwand, I., and Duryee, A. W.: Scleroderma: diffuse disease of the collagen system, report of 145 cases (to be published).
19. Touraine, A., Gole, L., and Soulignac, R. R.: La cellulite sclerodermiforme extensive bénigne. Scléroedème de Buschke, *Ann. de dermat. et syph.* 8: 761-800, 1937.

CEREBRAL SCHISTOSOMIASIS: REPORT OF CASE WITH MEDICAL MANAGEMENT *

BY HERBERT SALIS, M.D., *Philadelphia, Pennsylvania*, and WAYNE C.
SMITH, M.D., *Ashland, Ohio*

CEREBRAL schistosomiasis is a rare complication of schistosomiasis japonica. In the past three years, however, there has been an increase in reported cases of this complication, primarily because of the exposure of American troops to the cercaria-infested waters of the island of Leyte. A comprehensive survey of many of these, as well as of previous cases, has been made recently by Kane and Most.¹ In many of these reports, the correct diagnosis was established only after operative intervention for a space-occupying lesion in the cerebrum. Moreover, craniotomy with operative removal of the mass, followed by a course of antimony, has been recommended as treatment for this complication.^{2, 3} Such surgical procedure has produced residual neurologic abnormalities. We therefore present a case report

* Received for publication February 12, 1949.

From the Medical Service, Crile Veterans Administration Hospital, Cleveland, Ohio.

Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

The authors are indebted to Dr. Joseph M. Hayman, Jr. and Dr. Norman P. Shumway for their encouragement, aid and advice in the management of this case.

of cerebral schistosomiasis in which the diagnosis and treatment have been through medical means alone, with resultant complete recovery.

CASE REPORT

On November 25, 1946, a 21 year old white male was admitted, because of epileptiform seizures, to the Neuropsychiatric Service of Crile Veterans Administration Hospital. From October 25, 1944, until early spring, 1945, while in the Army he had served on Leyte as a pipeline walker with a petroleum distribution company. Along his route there were numerous signs warning of the danger of schistosomiasis, but because of the nature of his work he was unable to avoid exposure. During this period of time he suffered only from a brief episode of mild diarrhea. In February, 1946, he was discharged from the Army.

The patient was asymptomatic until early September, 1946, when he awoke one morning to find he had bitten his tongue. Five days later his father noticed him staring and thought him to be mentally confused. On October 7, 1946, he developed a clonus of the left shoulder with jerking of the head to the right, followed by a period of unconsciousness of unknown duration. A dislocation of the left shoulder and an occipital laceration were sustained in the resulting fall. A few days later he was observed to convulse in his sleep. Minor seizures, of Jacksonian nature, recurred, sometimes preceded by a blurring of near vision. On November 5, 1946, he was seen at a clinic where an electroencephalogram suggested a focal abnormality in the right frontal region. At that time some hyperemia of the left optic disc and some exaggeration of the reflexes of the left arm were found. The impression was that a Jacksonian focus existed in the arm area of the right cerebral hemisphere. He was started on phenobarbital and diphenylhydantoin sodium therapy. Two weeks prior to admission severe prefrontal headaches were noted, during one of which there was a spontaneous nystagmus.

After admission to the hospital the patient remained asymptomatic for six weeks, although anti-convulsive therapy was discontinued. It was observed that he portrayed symptoms of a mild psychoneurosis, including emotional instability and fear of crowds. There was no history of previous epilepsy, and the family history was negative for any epileptic state. No significant abnormalities were found upon physical examination. Blood counts were normal except for an eosinophilia of 2 to 16 per cent. Repeated stool examinations for *Schistosoma* ova were negative. An electroencephalogram performed soon after admission revealed a diffuse cortical dysfunction with no evidence of localization. Spinal fluid examination revealed no abnormalities other than some increased pressure, and skull roentgen-rays and a pneumoencephalogram were normal. A psychometric examination, including the Rorschach test, demonstrated a marked schizoid tendency and spotty organic signs of encephalopathy.

On January 1, 1947, a convulsive seizure involved the right hand, arm and face. Five days later the patient experienced Jacksonian fits involving alternately the right and the left side of the body and associated with a brief period of unconsciousness. He was started on phenobarbital 0.03 gm. and diphenylhydantoin 0.1 gm., three times daily, and no further convulsions occurred. On February 28, 1947, a skin test of 0.1 c.c. of 1:8,000 dilution of cercarial antigen, procured from the Army Medical Center, Washington, D. C., was performed and interpreted as being positive. A complement fixation test for schistosomiasis, performed at the National Institutes of Health, Bethesda, Maryland, was reported as giving an anticomplementary reaction. In a proctoscopic examination, a small white plaque about 1 mm. in diameter was observed in the rectosigmoid. Repeat proctoscopy several days later for biopsy purposes failed to rediscover the plaque. Upon discontinuance of the phenobarbital and reduction of

the diphenylhydantoin to 0.1 gm. twice daily, symptoms recurred and continued despite a return to the original dosage of the latter drug. An attempt to perform a visual fields examination failed because of interrupting Jacksonian seizures, but possible minimal disc edema of the left eye was reported.

On March 12, 1947, the patient was seen by Dr. Charles A. Kane, Lakeside Hospital, Cleveland, Ohio. The consultant's impression was schistosomiasis japonica, latent phase, with secondary encephalopathy. He recommended a full course of intravenous tartar emetic therapy. The patient thereupon was transferred to a medical ward. Treatment was started on March 20, 1947, and was discontinued on March 28 because of Jacksonian convulsions of increasing frequency, some in alarmingly rapid succession. These attacks, requiring the re-institution of phenobarbital therapy, were considered to be due to either the direct action of the antimony compound or the use of an autoclaved solution. Injections were resumed on April 4 with a non-autoclaved sterile solution, and no convulsive seizures occurred thereafter. The treatment consisted of intravenous injections on alternate days of a 0.5 per cent sterile solution of antimony and potassium tartrate, beginning with 8 c.c., increasing by 4 c.c. until 28 c.c. were reached, and continuing on that dose for a full course of 444 c.c., or 2.22 gm. The last injection was performed on May 9, 1947. The injections were given very slowly, requiring 10 to 25 minutes for completion, with the patient remaining recumbent for at least an hour afterward. Reactions to the therapy consisted of marked local phlebitis at the site of injection, an occasional irritative cough immediately after injection, an episode of nausea, vomiting and diarrhea occurring about one hour after the injection and lasting for about one hour, an episode of pruritic erythema on the left upper arm, and a metallic taste after the last three doses. An electrocardiogram on May 12 showed an abnormal record, with flat to inverted T waves in all limb leads, V_2 and V_4 . A repeat electrocardiogram on June 4, 26 days after therapy, reported a return to normal of the T waves, with the impression that the previous findings had been due to drug therapy.

The phenobarbital and diphenylhydantoin had been steadily reduced in dosage and entirely discontinued by May 19, 1947. An electroencephalogram on the following day still showed a generalized cerebral dysrhythmia. The patient remained asymptomatic and was discharged June 10, 1947.

On September 23, 1947, he returned for reexamination. There had been no convulsive seizures, the physical examination was normal, no eosinophilia was present, and he "enjoyed being well." A complement fixation test for schistosomiasis, performed at the National Institutes of Health, was reported negative on September 30, 1947.

The patient was readmitted on January 18, 1948, for a six-month post-therapeutic examination. He had had only two momentary spells of nodding of the head, induced by intermingling with the crowds of downtown Cleveland. He had always shown a fear of crowds. Physical examination revealed no abnormalities. The psychometric examinations of December 13, 1946 were repeated. The Rorschach test showed marked improvement in the intellectual sphere, as indicated by the patient being more practical, better able to organize his thoughts, and losing his tendency to overemphasize and to stress the inconsequential. His previous schizoid and organic signs had disappeared. An electroencephalogram performed on January 9, 1948 was normal. On January 27, 1948, a skin test employing cercarial antigen of 1:8,000 dilution was negative. He was discharged, and when seen briefly on February 27, 1948, he was still asymptomatic.

On August 30, 1948, the patient entered the hospital for another routine re-evaluation, 14 months after his original discharge. Except for his usual neurotic complaints, he had been doing well and was prepared to enter a local college whose entrance examinations he had passed. There had been no headaches, convulsions

or other neurologic manifestations. Physical examination was not remarkable and routine laboratory work, serum proteins, and spinal fluid studies were all within normal limits. An electroencephalogram was normal, and a complement fixation test for schistosomiasis was reported to be negative. Psychometric testing this time showed a return of organic signs of encephalopathy, of somewhat diffuse nature and more conclusive than those prior to treatment. His intellectual functions had improved, however. The organic signs were believed due to cerebral scarring. The patient's stay was uneventful and he was discharged September 3, 1948.

DISCUSSION

In 22 reported cases of latent, or chronic, schistosomiasis japonica with cerebral involvement, the diagnosis was established in 15 cases by craniotomy with biopsy^{2, 3, 4} and in five cases by autopsy.⁵ In the remaining two cases, the diagnosis was inferred on the basis of *Schistosoma* ova in the stools and a beneficial response to antimony therapy.^{5, 6}

By medical investigation, a diagnosis of cerebral schistosomiasis may be made without resort to surgery. Of great importance is the combination of a history of a definite exposure to the disease, with or without acute symptoms, and the presence of Jacksonian convulsions.^{2, 3, 4th} In our patient, additional diagnostic aids included a positive skin reaction to 1:8,000 cercarial antigen, abnormal electroencephalograms, evidence of increased intracranial pressure, mental deterioration demonstrated by psychometric testing, and a low-grade eosinophilia. *Schistosoma* ova were absent in the stools, and the complement fixation test gave an anti-complementary reaction. The diagnosis was further confirmed by post-therapeutic changes. Epileptiform seizures did not recur and, after eight months, the electroencephalogram was normal. After approximately the same period of time, a repetition of the skin test was negative. This compares favorably with the findings of others, who considered this reversal of the skin test to be a demonstration of adequate treatment.^{7, 8} Furthermore, there was dramatic improvement in the psychometric examinations performed at that time, with complete disappearance of previous organic signs (their later return is believed indicative of post-therapeutic cicatrization).

It is interesting that the first electroencephalogram showed a focal abnormality in the right frontal area at a time when the patient's symptoms were comparatively mild. Later, after an electroencephalogram revealed a diffuse cortical dysrhythmia with no localization, the patient's condition became progressively worse. These findings would appear to conform to the embolic theory of cerebral involvement by *Schistosoma japonica*.

SUMMARY

1. A case of latent, or chronic, schistosomiasis japonica, with cerebral involvement, is reported.
2. The diagnosis was established by a history of exposure to the disease, a symptom complex including Jacksonian convulsions, a positive skin test to cercarial antigen, a low-grade eosinophilia, abnormal electroencephalograms, and psychometric evidence of mental deterioration.
3. Confirmation of the diagnosis was furnished by a cessation of symptoms with therapy, a subsequent return to normal of the skin test and electroencephalo-

gram, and by marked mental improvement as evidenced by psychometric examination.

4. Therapy consisted of a sterile 0.5 per cent solution of potassium and antimony tartrate injected intravenously, with a total dosage of 444 c.c., or 2.22 gm.

5. Reactions to the drug therapy consisted of a marked local phlebitis, occasional immediate cough, an episode of nausea, vomiting and diarrhea one hour after injection, appearance of a pruritic erythema, and a metallic taste following the final three injections. There were also temporary changes in the T waves of the electrocardiogram.

6. Medical diagnosis and therapy have resulted in complete recovery in a case of cerebral schistosomiasis.

BIBLIOGRAPHY

1. Kane, C. A., and Most, H.: Schistosomiasis of the central nervous system. Experiences in World War II and a review of the literature, *Arch. Neurol. and Psychiat.* **59**: 141-183 (Feb.) 1948.
2. Greenfield, J. G., and Pritchard, B.: Cerebral infection with *Schistosoma japonicum*, *Brain* **60**: 361-372 (Sept.) 1937. (One case previously reported by Edgar.^{4b})
3. Chang, T., Smith, G. W., Riesenman, F. R., and Alston, E. F.: Cerebral granuloma due to schistosomiasis, *J. A. M. A.* **136**: 230-238 (Jan. 24) 1948.
4. (a) Shimidzu, K.: Ein Operationsfall von Schistosomiasis cerebri, *Arch. f. klin. Chir.* **182**: 401-407, 1935; cited by Spiegel.^{4a}
 (b) Edgar, W. H.: Report on case of epilepsy due to infection by *Schistosomum japonicum*, *J. Roy. Nav. M. Serv.* **22**: 150-153 (April) 1936.
 (c) Swanson, H. S.: Cerebral granuloma due to schistosomiasis japonica, a case report, *J. Neurosurg.* **3**: 538-542 (Nov.) 1946.
 (d) Spiegel, I. J.: Cerebral schistosomiasis: report of a case with surgical removal of an intracerebral mass of *Schistosoma* ova, *J. Neurosurg.* **4**: 72-79 (Jan.) 1947.
 (e) Watson, C. W., Murphy, F., and Little, S. C.: Schistosomiasis of the brain due to *Schistosoma japonica*, *Arch. Neurol. and Psychiat.* **57**: 199-211 (Feb.) 1947.
 (f) Chasnoff, J.: Personal communication to Watson, Murphy and Little.^{4c}
 (g) Maltby, G. L., and Smith, J. R.: Schistosomiasis of the cerebrum simulating brain tumor, to be published; cited by Watson, Murphy and Little.^{4c}
 (h) Reeves, D. L., and Kerr, R. W.: Schistosomiasis japonica with intracerebral granuloma: operative removal with recovery, *Arch. Neurol. and Psychiat.* **58**: 207-220 (Aug.) 1947.
 (i) Hunt, W. E., Abramson, E., and Weaver, T. A.: Cerebral schistosomiasis, *J. A. M. A.* **136**: 686-689 (March 6) 1948.
 (j) Saunders, G. M.: Personal communication to Chang.³
5. (a) Tsunoda, T., and Schimamura, S.: Pathology of Katayama disease: supplementary report on the cause of Jacksonian epilepsy and emboli of the cerebral artery, *Kyoto Igakkwai Zasshi* **2**, No. 3, 1905; cited by Carroll, D. G.: Cerebral involvement in schistosomiasis japonica, *Bull. Johns Hopkins Hosp.* **78**: 219-234, 1946.
 (b) Yamagiwa, K.: Contribution to the etiology of Jacksonian epilepsy. The pathological changes of the cerebral cortex caused by *Distoma* eggs, *J. Tokyo M. A.* **1889**, III (No. 18); cited by Carroll.^{5a}
 (c) Africa, C. M., and Santa Cruz, J.: Eggs of *Schistosoma japonicum* in the human heart, in *Volumin Jubilare pro Sadao Yoshida*, Osaka, Japan **2**: 113-117, 1939; cited by Chang et al.³
 (d) Vitug, W., Cruz, J. R., and Bautista, L. D.: Schistosomiasis involving the brain: two cases, *J. Philippine M. A.* **21**: 291-298 (June) 1941.

6. Nieva, D. E.: Epileptiform convulsions probably due to schistosomiasis, *Bull. San Juan de Dios Hosp.* 9: 234-237 (July) 1935.
7. Katzin, B., and Most, H.: Cercarial antigen (*S. Mansoni*) skin test in diagnosis and management of schistosomiasis japonica, *Bull. U. S. Army M. Dept.* 6: 613-616, 1946.
8. Alves, W., and Blair, D. M.: Schistosomiasis; intensive treatment with antimony, *Lancet* 1: 9 (Jan. 5) 1946.

RECURRENT ACUTE LUPUS ERYTHEMATOSUS DISSEMINATUS: REPORT OF A CASE WHICH HAS SURVIVED TWENTY-THREE YEARS AFTER THE ONSET OF SYSTEMIC MANIFESTATIONS *

By SOLOMON BEN-ASHER, M.D.,† *Jersey City, New Jersey*

ACUTE disseminated lupus erythematosus is a systemic disease of multiform character, often manifested by erythematous lesions, prolonged fever, polyarthritides, endocarditis, nephritis, polyserositis, leukopenia and anemia. The primary organic changes, as described by Klemperer,¹ consist of an involvement of the collagen and ground substance of the connective tissue.

The disease has a marked predilection for females and is most common in the second and third decades. A striking characteristic is the tendency for cutaneous and systemic manifestations to appear or recur after exposure to sunlight, ultraviolet light and roentgen-rays, and also following gold and bismuth therapy. The onset of the disease may be abrupt, or it may be gradual with a general feeling of ill health and arthralgia. The most common cutaneous lesions appear on the face, but other parts may be involved, such as the extremities, particularly the hands, also the neck and the trunk. The rash may be diffusely red or it may be bluish red, raised and indurated. The lesions increase in size and have a tendency to coalesce to form large erythematous eruptions which at times exhibit areas of hemorrhage, papules and vesicles, crust formation and scaling. They may be painless, or there may be intense burning and pruritus. The prognosis is extremely grave. In some cases the systemic reactions are severe and the course is short, resulting in a fatal termination in a few weeks or months. In other cases the systemic reactions are mild, with remissions and exacerbations of variable duration and severity. These, too, usually terminate fatally within five years.

This report concerns a case of recurrent acute disseminated lupus erythematosus which has survived many years after the onset of constitutional symptoms. The patient also had abnormal urinary findings from which she recovered.

CASE REPORT

This 65 year old female first came under observation at 42 years of age on October 11, 1925. The previous history was essentially negative and the family

* Received for publication December 30, 1948.

From the Greenville Hospital and the Medical Center, Jersey City, New Jersey.

† Dr. Ben-Asher died on April 27, 1949.

history irrelevant. Examination at that time revealed a middle aged woman who was acutely ill. The temperature was 103.2° F., the pulse was 98 and the respirations were 22 per minute. The blood pressure was 130 mm. Hg systolic and 80 mm. diastolic. There was a butterfly lesion on the face and there were raised erythematous lesions on the chest and extremities. The blood showed a slight anemia and leukopenia. The urine was normal. She recovered and remained well and free of cutaneous lesions until March 1932, when she had a recurrence of skin eruption and fever. After a stormy course of four weeks, the patient recovered. Then followed another free interval until June, 1944, when, after an exposure to the sun, cutaneous lesions and fever reappeared. She was ill for a period of two weeks and recovered spontaneously.



FIG. 1. Erythematous lesions of face, neck and upper extremities. The upper extremities also show scaling.

Present Illness: The patient felt well and was free of skin lesions until May 4, 1945, when she noticed a recurrence of a facial eruption and had chills and fever. At the same time she also had pain all over the body, particularly in the knees, elbows and fingers. A few days later, eruptions appeared on the left ear and chin, followed by lesions on the neck, chest and extremities. The eruptions on the extremities were slightly tender and gave a burning sensation.

Physical examination revealed a well-developed and well-nourished woman who appeared acutely ill. The temperature was 104.4° F., the pulse 118, and the respirations 24 per minute. The blood pressure was 220 mm. Hg systolic and 116 mm. diastolic. The skin showed elevated erythematous lesions involving both cheeks, forehead, chin, left ear, neck, chest and extremities (figure 1). There was moderate

bilateral cervical adenopathy. The heart was enlarged to the left. The sounds were of good quality. The aortic second sound was louder than the pulmonic and the rhythm was regular. A grade 2 systolic murmur was heard over the apex. The lungs were clear to percussion and to auscultation. The liver and spleen were not palpable. The extremities showed the cutaneous lesions described above. The joints were normal. The fundi showed sclerosis of the retinal vessels; there were no exudate and no edema of the discs. The neurologic examination did not reveal any abnormalities.

Laboratory Data: The urine contained 3 plus albumin, no sugar, 4 to 5 white blood cells and 12 to 15 red blood cells per high power field. There were a few granular and hyaline casts. The specific gravity was 1.020. A blood count showed

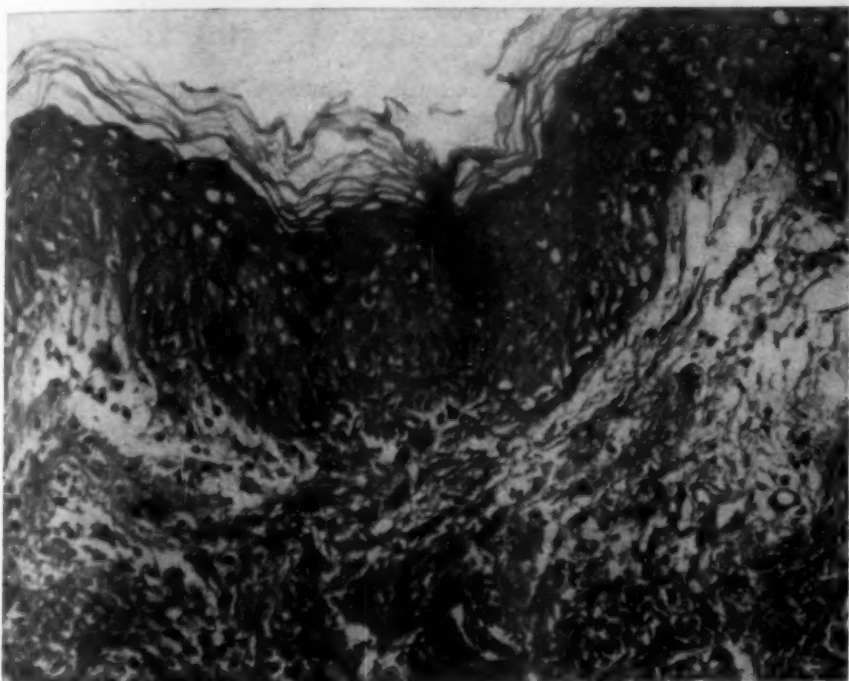


FIG. 2. Microscopic section of the forearm showing the histologic changes described in the text.

3,290,000 red blood cells and 4,200 white blood cells per cu. mm. The hemoglobin was 9.5 gm. per 100 c.c. A differential count showed: segmented neutrophils 41 per cent, nonsegmented neutrophils 12 per cent, eosinophils 2 per cent, lymphocytes 40 per cent, and monocytes 5 per cent. The non-protein nitrogen was 40 mg. per 100 c.c. and the blood sugar 112 mg. per 100 c.c. Blood cultures were sterile and serologic tests for syphilis were negative. A biopsy of the lesion of the left arm was made on May 16, 1945, with the following report:

Gross: "The tissue submitted consists of skin and muscle. The piece of skin measures 2 cm. in length by 4 mm. in width. There is underlying subcutaneous fat 1 cm. in thickness. The skin surface is white. The dermis is gray-white and translucent. The fat contains a reddened area.

"The other piece of tissue measures 1 by 0.7 by 0.3 cm. and 0.5 cm. in diameter, respectively. The larger piece presents a pink-tan translucent surface; the smaller presents pink-tan foci within fat."

Microscopic Examination (figure 2): "The stratified squamous epithelium is of average thickness. In some of its basal portions some of the nuclei are shrunken. The papillary layer of the dermis is markedly edematous and in many areas is infiltrated by lymphocytes and some polymorphonuclear leukocytes. In some foci there is swelling of the collagen, with infiltration by many polymorphonuclear leukocytes. Capillaries within these areas present thickened walls and are dilated. No frank necrosis of the capillary wall is present. Lymphocytic infiltration and some polymorphonuclear leukocytic infiltration extend around the capillaries into the reticular layer of the corium. Near one resected edge of the skin there is an extension of the inflammatory elements around the hair follicles. Adjacent to this, inflammatory cells extend into the reticular layer of the dermis in large numbers. Within the subcutaneous fat there are small numbers of lymphocytes, scattered polymorphonuclear leukocytes, and small numbers of mononuclear histiocytic cells. There is swelling of the collagen of a venule near the deep line of resection. Superficial to the markedly edematous portions of the papillaris there is infiltration by some lymphocytes and a few polymorphonuclear leukocytes into the deeper portions of the epidermis. In these regions there is edema between the epidermal cells. The piece of striated muscle tissue is without significant change, except for small foci of fibroblastic proliferation within the loose fibrous tissue between the muscle bundles. The picture is compatible with a diagnosis of acute lupus erythematosus."

Course: During the first week, more erythematous lesions appeared on the extremities and the chest. Some of the lesions coalesced to form large erythematous eruptions with scaling. The temperature remained elevated and ranged from 100.2° F. to 103.8° F. and was septic in type. Throughout the course, albumin, red cells and casts persisted in the urine. The blood showed a persistent leukopenia, the white cells varying from 4,200 to 5,400. The blood pressure remained elevated. The patient was given 100,000 units of penicillin every two hours. On May 15, the patient became worse and appeared critically ill. The temperature reached 105.2° F.; pulse was 146 and respirations were 28. On May 22 the patient showed marked improvement. On May 25 the temperature became normal, and the eruption began to fade and finally disappeared completely. Examination of several urinary specimens revealed no abnormal findings. On June 27, 1945, the patient had an attack of coronary occlusion with anterior myocardial infarction from which she made an uneventful recovery. Subsequently, the patient failed to return for observation. A follow-up disclosed that she had a recurrence of cutaneous lesions and fever in October, 1946, and again in June, 1947. There were no abnormal urinary findings then. When last seen on October 29, 1948, the patient appeared well.

COMMENT

The case herein described presents a number of interesting features. While it is realized that the clinical and pathologic diagnosis of disseminated lupus erythematosus is often difficult, the diagnosis is justified in this case because of the typical cutaneous lesions, severe systemic reaction, leukopenia, abnormal urinary findings, and also the characteristic histologic picture. It may be noted that this patient later developed hypertension and coronary occlusion. Coronary occlusion is unknown in disseminated lupus erythematosus. Hypertension was found to be uncommon in the cases reported by Baehr, Klemperer and Schiffrin,² but was found to be present in one-third of the cases reported by Rose

and Pillsbury.³ Ginzler and Fox⁴ described a case of disseminated lupus erythematosus in a 17 year old male in whom hypertension was observed to have developed. Since our patient had already reached the end of the fifth decade, a correlation between the disease and the development of the hypertension and the coronary occlusion is questionable.

Of particular interest in this case are the duration of survival and the recurrence of the disease over many years. As is well known, the diagnosis of acute disseminated lupus erythematosus carries with it a fatal prognosis. In 30 patients with the disease reported by Montgomery,⁵ the mortality rate was 100 per cent. Rose and Pillsbury⁶ also found a mortality rate of 100 per cent in 13 cases. Reifenstein and his associates⁷ stated that the duration of the disease from the onset of constitutional symptoms is four and one-half to 48 months, the average being 18 months. The patient described above is alive 23 years after the onset of the disease. A search of the literature reveals this to be the greatest duration of the disease to be recorded. In the recurrence above recorded the patient appeared moribund. She was treated with penicillin and recovered. The question arises whether the recovery could be attributed to the chemotherapy. However, one occasionally sees a spontaneous remission in a patient who appears moribund. Furthermore, on previous occasions the patient had improved spontaneously. It would seem, therefore, that the recovery probably was not attributable to the chemotherapy.

The urinary findings in this case are also of interest. Renal involvement is common in acute lupus erythematosus. The characteristic kidney lesion as described by Baehr and his associates² has a "wire-loop" appearance, which is due either to the hyaline thickening of the walls of the glomerular capillaries, or to fibrinoid degeneration and collagenization of the basement membrane. Stickney and Keith⁸ also found a proliferation of the endothelial cells of the glomerular capillaries. Despite the renal involvement, renal insufficiency, according to Stickney,⁹ does not play an important rôle in causing death. Since in some cases albuminuria may vary periodically from grade 1 to grade 4, and yet at necropsy only minor histologic changes in the glomerulus be found, the author suggested that the renal lesion may be temporarily reversible. Rose and Pillsbury,⁶ on the other hand, found terminal renal failure strikingly frequent. Kiel¹⁰ also found that evidence of renal involvement is an indication of a fatal prognosis in the immediate attack, although he observed temporary improvement in a few instances. The patient described above had abnormal urinary findings consisting of albuminuria, red cells and casts which disappeared when the patient recovered. The patient is alive four years after the appearance of abnormal urinary findings.

SUMMARY

A case is presented of recurrent acute disseminated lupus erythematosus that has survived 23 years after the onset of constitutional manifestations. The patient had abnormal urinary findings from which she recovered and which did not reappear during the following four years. As far as it is known, this is the longest duration of life to be recorded in this disease.

The author wishes to express his appreciation to Dr. E. A. P. Peters for performing the biopsy and to Dr. A. Gitlitz for examination of the pathologic specimen.

BIBLIOGRAPHY

1. Klemperer, P.: The pathogenesis of lupus erythematosus and allied conditions, *Ann. Int. Med.* 28: 1, 1948.
2. Baehr, G., Klemperer, P., and Schiffrin, A.: Diffuse disease of peripheral circulation usually associated with lupus erythematosus and endocarditis, *Trans. A. Am. Physicians* 1: 193, 1935.
3. Rose, E., and Pillsbury, D. M.: Acute disseminated lupus erythematosus, a systemic disease, *Ann. Int. Med.* 12: 951, 1939.
4. Ginzler, A. M., and Fox, T. T.: Disseminated lupus erythematosus, a cutaneous manifestation of a systemic disease (Libman-Sacks); report of a case, *Arch. Int. Med.* 65: 26, 1940.
5. Montgomery, H.: Symposium on lupus erythematosus, *Proc. Staff Meet., Mayo Clin.* 15: 678, 1940.
6. Rose, E., and Pillsbury, D.: Lupus erythematosus (erythematoses) and ovarian function: observations on a possible relationship with report of six cases, *Ann. Int. Med.* 21: 1022, 1944.
7. Reifstein, E. C., Reifstein, E. C., Jr., and Reifstein, G. H.: A variable symptom complex of undetermined etiology with fatal termination, including conditions described as visceral erythema group (Osler), disseminated lupus erythematosus, atypical verrucous endocarditis (Libman-Sacks), fever of unknown origin (Christian), and diffuse peripheral vascular disease (Baehr and others), *Arch. Int. Med.* 63: 553, 1939.
8. Stickney, J. M., and Keith, N. M.: Renal involvement in disseminated lupus erythematosus, *Arch. Int. Med.* 66: 643, 1940.
9. Stickney, J. M.: Symposium on lupus erythematosus, *Proc. Staff Meet., Mayo Clin.* 15: 678, 1940.
10. Kiel, H.: Dermatomyositis and systemic lupus erythematosus: a comparative study of the essential clinicopathologic features, *Arch. Int. Med.* 66: 339, 1940.

MYOCARDIAL CONTUSION: THE REPORT OF A FATAL CASE WITH AUTOPSY *

By HORACE H. HODGES, M.D., F.A.C.P. and MONROE T. GILMOUR, M.D., F.A.C.P., *Charlotte, North Carolina*

MYOCARDIAL contusion probably occurs more frequently than is yet generally recognized.^{1, 2, 3, 4, 5, 6, 7, 8} In the management of chest trauma, it is important to recognize early the presence of cardiac injury. Its occurrence should be suspected in all cases of chest trauma even when no penetrating wound is present. The following case report illustrates the recognition of this cardiac injury. The fatal outcome, which may have been influenced in part by a delay in diagnosis, stimulates us to present this case in the hope of increasing the general alertness to the occurrence of severe cardiac injury in the absence of penetrating chest wounds.

* Received for publication December 9, 1948.

Presented at the Regional Meeting of The American College of Physicians, Durham, N. C., December 3, 1948.

The photographic prints of the electrocardiograms, and the photomicrographs were prepared by the Heineman Foundation, Charlotte, N. C.

CASE REPORT

A 59 year old white man was injured in an automobile accident on September 7, 1947. In the head-on collision, his body was thrown against the steering wheel with such force that the steering wheel was broken. Subsequently, he was admitted and held for observation in a small private clinic in another town. The physical and fluoroscopic examinations revealed the presence of multiple bilateral rib fractures and a fracture of the right clavicle. For the first 24 hours after the accident, he was afebrile and ambulatory. During this time he complained of mild to moderate anterior chest pain. At the end of the first 24 hours, the chest pain increased and

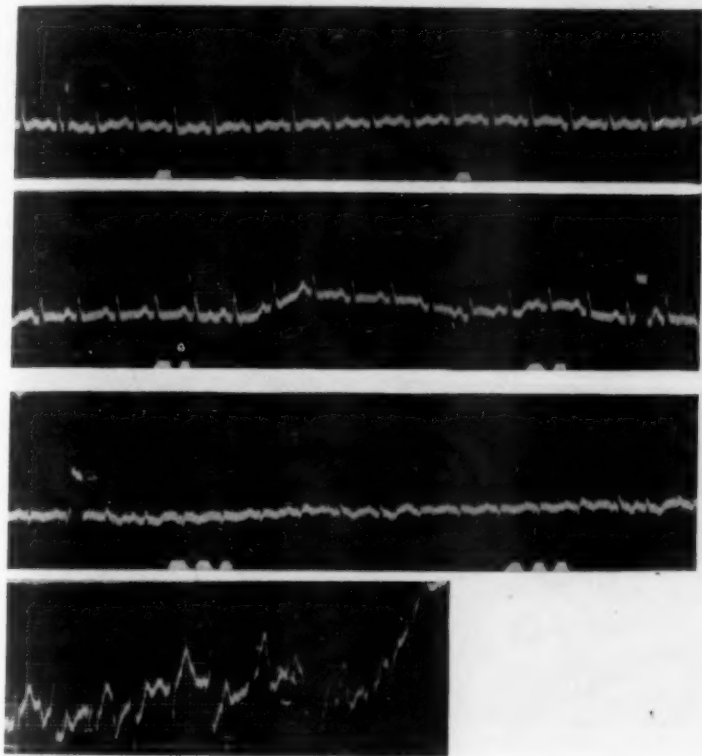


FIG. 1.

the temperature became elevated to 100° F. At this time the administration of sulfadiazine was begun. The temperature continued to rise and on the second day after the accident, September 9, he became irrational. The chest pain became more severe. Cramps in the legs, abdominal discomfort and abdominal distention appeared. Shortly thereafter he became dyspneic and cyanotic. Three cat units of Digiglusin were then given intravenously, and he was transferred by ambulance to the Charlotte Memorial Hospital.

On admission at 10:15 p.m., September 9, 1947, approximately 54 hours after injury, he was severely dyspneic, cyanotic and comatose. His temperature was 104° F. rectally, his respirations 40 per minute and his pulse rapid. Blood pressure varied from 120 mm. Hg systolic and 80 mm. diastolic to 150 mm. Hg systolic and 80 mm.

diastolic and was difficult to obtain. He was heavily built and moderately overweight. A minor laceration was present over the right forehead and there was a contusion over the right clavicle. No other evidence of soft tissue injury over the thorax was noted. His respiration was extremely labored, and gross rhonchi were audible without the stethoscope. Auscultation revealed, in addition, many wheezes and a few fine moist râles throughout the lung fields, but percussion was normal. The trachea was in the midline and there was no evidence of displacement of other mediastinal structures. The heart sounds were rapid, approximately 152 per minute, pounding and regular. No murmurs or friction rubs were audible. The abdomen was distended and tympanitic. Further examination was not done on admission because of

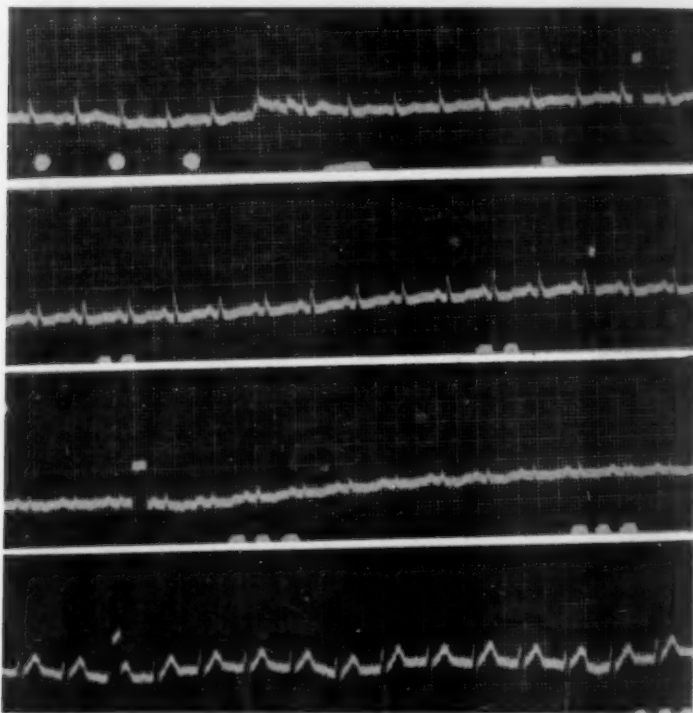


FIG. 2.

his critical condition. Subsequently, examination of the upper respiratory passages, eyes, head, lymphatic and musculoskeletal systems revealed no finding of significance. Repeated neurologic examinations failed to suggest intracranial injury. On admission, a presumptive diagnosis of myocardial contusion with cardiac decompensation was made and energetic therapeutic measures were initiated. Oxygen inhalation by B.L.B. mask at the rate of 8 to 10 liters per minute was begun immediately, and shortly thereafter he received morphine sulfate grains 1/6th and atropine sulfate grains 1/150th hypodermically. The administration of penicillin was also started at this time. He appeared to be in imminent danger of death. Within the next hour a phlebotomy was done, with the rapid removal of 500 c.c. of blood. Blood pressure cuffs were then placed on all extremities and inflated just above the diastolic pressure.

A rectal suppository containing 0.5 gm. aminophylline was inserted. One c.c. Coramine, 1.0 c.c. Mercuzanthin and 0.4 mg. Purodigin were administered intravenously. Also, during the first hour after admission, the initial electrocardiogram was secured and revealed a regular rate of 150 with an isoelectric T_a (figure 1). A portable roentgenogram of the chest revealed numerous ill-defined nonhomogeneous densities throughout the left chest. The left diaphragm could not be identified. By 10:00 a.m. on the morning following admission, the third day after the injury, considerable improvement had occurred. Consciousness had returned and he was able to take fluids, recognize familiar persons and respond coherently to questioning. An electrocardiogram at this time revealed no changes as compared with that of the previous

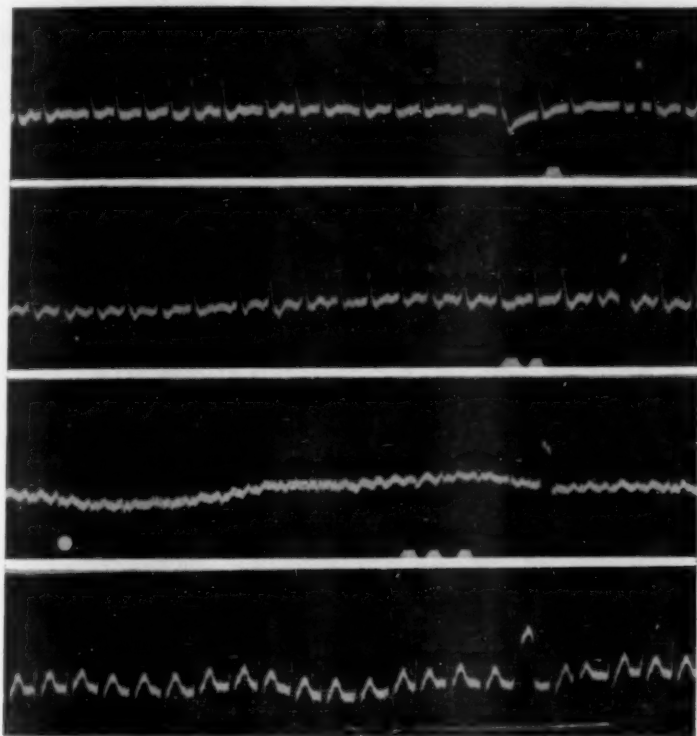


FIG. 3.

day (figure 2). The pulse remained about 150 and blood pressure about 140 mm. Hg systolic and 90 mm. diastolic. At this time, 0.4 mg. Purodigin was given intravenously. At 12:30 p.m. he became restless and received hypodermically 2 grains of sodium luminal. Following this, his pulse became weaker and irregular. The oral administration of quinidine sulfate, 0.2 gm. four times a day, was begun. Disorientation, profuse perspiration, increased dyspnea and cyanosis reappeared. At 1:10 p.m., blood pressure was questionably obtainable at 120 mm. Hg systolic and 90 mm. diastolic. Coramine and caffeine intravenously and aminophylline rectally had little apparent effect. An electrocardiogram at this time revealed impure auricular fibrillation (figure 3). Following this episode, his condition deteriorated progressively. Fever gradually increased in spite of large doses of penicillin. The blood pressure

varied from 100 to 200 systolic. After September 11, the fourth day after injury and second day after admission, he remained comatose and at times was extremely restless. Hydration and medication were of necessity maintained parenterally and with great care. Intravenous administration of fluid was avoided because of the fear of increasing the burden on the right side of the heart. Extreme dyspnea, cyanosis and pulmonary edema persisted. A portable roentgenogram on the morning of September 13 showed some general improvement in the lung fields, but spotty shadows were present and a zone of lobular atelectasis was seen on the right. Death occurred during the afternoon of September 13, 1947, on the fourth hospital day and the sixth day after the accident.

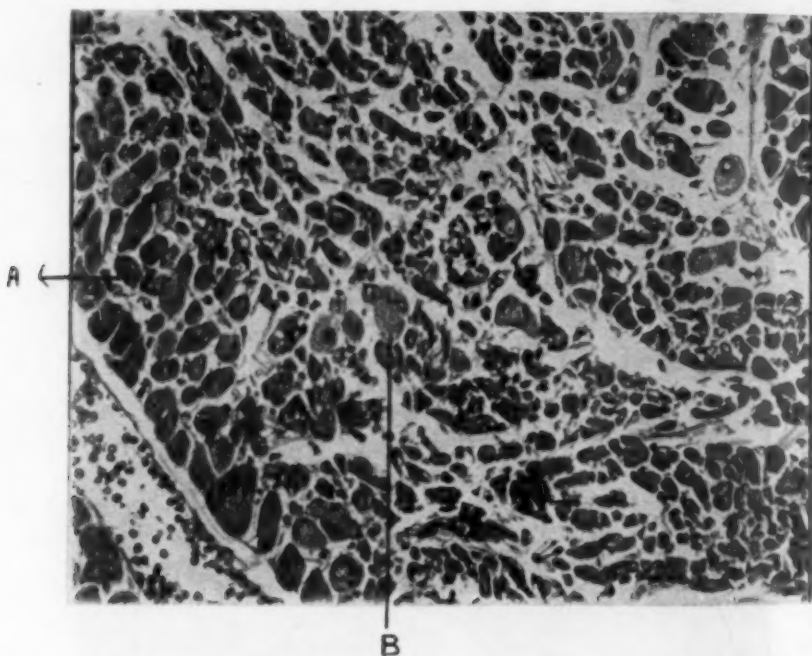


FIG. 4. Low power showing an area of myocardium with normal heart muscle fibers (A). In comparison are swollen, vacuolated disintegrated fibers with various stages of fragmentation (B).

Other laboratory data were not remarkable. The initial blood count revealed 14,000 leukocytes, 4.63 million erythrocytes, and 13.0 gm. of hemoglobin per c.c., and the hematocrit was 46 per cent. On September 12, the number of leukocytes had risen to 19,200 per c.c. Urinalyses on September 10 and September 12 revealed 1 plus albumin, with 1 to 3 erythrocytes and 8 to 20 granular casts per high power field. Blood Wassermann and Kahn reactions were negative. On September 10, the blood urea nitrogen was 32 mg. per cent and the blood sugar was 117 mg. per cent. On September 13, blood culture was negative and blood agglutinations for enteric pathogens, *Brucella* and *Pasteurella tularensis* were likewise negative.

The postmortem examination* revealed findings of significance only in the thorax. There were fractures of the right clavicle, the upper six ribs in the left anterior axillary line and the upper five ribs in the right anterior axillary line. Diffuse and extensive hemorrhages were present in the anterior mediastinum.

* From the Department of Pathology of the Charlotte Memorial Hospital.

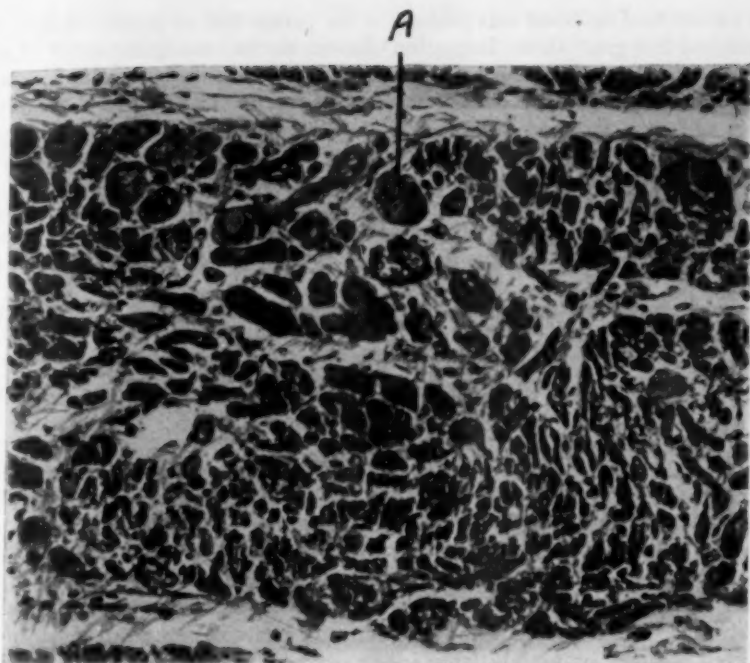


FIG. 5. In an area of myocardium different from that shown in figure 1 are similar changes of swelling, disintegration and fragmentation (A).

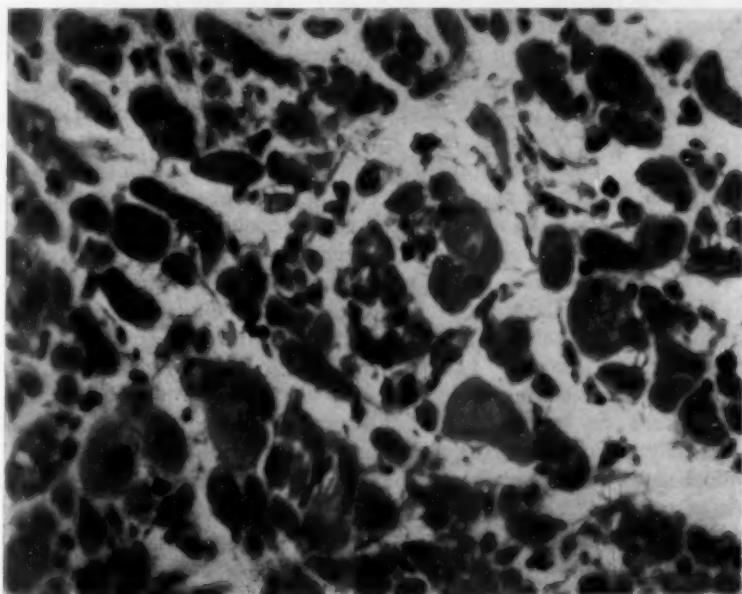


FIG. 6. Higher power showing, in addition to changes seen in figures 1 and 2, interstitial infiltration with a variety of small round cells.

No excess fluid or blood was present in the pericardial or pleural cavities. The heart weighed 390 gm. Gross inspection showed normal configuration of all chambers. The valvular apparatus, epicardium, endocardium and myocardium were normal. Dissection of coronary vessels revealed normal patency throughout the coronary tree.

Microscopic examination, however, showed multiple foci of necrosis distributed irregularly throughout the wall of the left ventricle. The foci of necrosis were characterized by partial or complete loss of cross striation, collapse of sarcoplasm, disintegration of muscle fibers, degenerative changes and loss of nuclei. Some of the foci of necrosis were accompanied by hemorrhages, but no inflammatory reaction was noticeable.

It was of particular interest to note the conspicuous absence of changes in the wall of the right ventricle.

Bronchopneumonic consolidations were present in the right lower lung. No gross or microscopic changes of significance were found in the brain or other organs.

DISCUSSION

Mode of Injury: There are several ways in which injury to the heart may occur.^{1, 2} The penetrating thoracic injuries do not concern us in this report. Non-penetrating injuries to the chest, with or without rib fracture, whether occurring directly over the precordium or not, may produce injury to the heart in a variety of manners. There may be a direct or a contrecoup contusion injury to the myocardium. Sigler³ has reported a high incidence of heart injury resulting from force transmitted entirely or mainly from other parts of the body. There may be an injury to a coronary vessel with resultant ischemia. Rupture of a heart valve or a papillary muscle occurs less frequently. Probably the most frequent type of injury is the automobile steering wheel chest contusion.

Diagnosis: Every person who has had a significant chest injury should be suspected of having sustained cardiac injury. Some authors³ have reported an incidence of cardiac contusion as high as 75 per cent in severe chest injuries. Some of these diagnoses perhaps have been based on insufficient evidence. The definitive antemortem diagnosis rests upon clinical data and serial electrocardiographic changes. The development of clinical signs is frequently delayed 24 hours or more. Electrocardiographic changes may be delayed and transient. It is therefore important in all suspected cases to obtain promptly a "base-line" electrocardiogram with chest leads. Clinical signs consist of disturbances of cardiac rhythm and function. Pain may be prominent or minimal. When present, it is characteristically substernal in location. Tachycardia, extrasystoles or auricular fibrillation may occur. Symptoms of varying degrees of cardiac decompensation may develop. The patient may go into sudden and unexpected cardiovascular collapse after getting along well for two or three days. On the other hand, there may be relatively mild discomfort, cough, dyspnea or orthopnea. Symptoms may be so mild that the cardiac injury is not suspected.

Physical signs vary from none to many. When present, the physical signs are those of cardiac arrhythmia, decreased cardiac function, or both. Auscultatory findings may include a friction rub, gallop rhythm, changing murmurs and variation in the character of the heart sounds. Signs of cardiac decompensation occur in all grades of severity. There may be mild dyspnea and orthopnea with a few basal lung râles, or there may be extreme pulmonary congestion with cy-

anosis, unconsciousness, et cetera. The significant electrocardiographic changes consist of the development of abnormal rhythms, conduction abnormalities, and changes in the ST segments and T waves. The inversion of the T waves in Leads I and II, changing A-V or intraventricular block and ST segment deviations exceeding 2 mm. in the limb leads are the most significant changes. The development of abnormal rhythms, ST segment and T wave changes in chest leads, changes in the QRS complexes, and limb lead changes of less degree than mentioned above are important in substantiating the suspicion of cardiac contusion in the presence of suggestive symptoms and signs. None of the electrocardiographic changes, however, is specifically diagnostic of cardiac contusion. The changes simply indicate myocardial damage.

Management: Any patient with significant chest injury or serious injury to other parts of the body should be kept at rest under observation with the suspicion of cardiac contusion. The occurrence of any symptoms or findings suggesting this condition demands absolute bed rest, even to the extent of having the patient fed. Upon recovery from the acute phase, the period of bed rest should be prolonged in proportion to the gravity of the cardiac injury. In such cases, re-activation might follow one of the plans used for myocardial infarction due to coronary occlusion. Bed rest in the severe cases should be continued for a minimum of four weeks, following which resumption of activity is undertaken very gradually. The occurrence of an abnormal rhythm is an indication for the use of quinidine in full therapeutic dosage. The frequency with which abnormal rhythms occur suggests that the routine prophylactic use of quinidine might be justified. The use of oxygen and vasodilator drugs such as papaverine, nicotinic acid, aminophylline, et cetera, is indicated regardless of the severity of symptoms in order to minimize the eventual myocardial necrosis. The appearance of cardiac decompensation calls for prompt and full digitalization, the use of mercurial diuretics, a low sodium diet, and other general measures. Phlebotomy is rarely necessary but may on occasions be life-saving. The use of tourniquets on all extremities, applied at a pressure between systolic and diastolic blood pressure to trap blood in the extremities, is a good temporary substitute for phlebotomy. The administration of intravenous cardiorespiratory stimulants is "heroic" and the necessity for their use indicates a very grave outlook.

Prognosis: The prognosis cannot be given accurately, for undoubtedly many cases of mild myocardial contusion are unrecognized. We believe that the large majority of patients survive the myocardial contusion. Sigler³ reports only one death in 42 cases and emphasizes the good prognosis.

SUMMARY

The increasing occurrence of cardiac contusion is becoming more and more apparent. It is important to recognize such cardiac injury early, so that proper therapeutic measures may be instituted promptly. The occurrence of substernal chest pain, cardiac arrhythmia, signs of cardiac decompensation and serial electrocardiographic changes in a patient with a recent chest injury calls attention to the possible presence of myocardial contusion. Such patients should be kept at complete bed rest and receive proper supportive treatment.

A fatal case of myocardial contusion exemplifying our concepts of the mode of injury, pathology, diagnosis and treatment has been presented.

BIBLIOGRAPHY

1. Bright, E. F., and Beck, C. S.: Nonpenetrating wounds of the heart, a clinical and experimental study, *Am. Heart J.* **10**: 293, 1934.
2. Sprague, H. B.: The effect of trauma and strain on the production and aggravation of heart disease, *Bull. New York Acad. Med.* **23**: 631-642 (Nov.) 1947.
3. Sigler, L. H.: Traumatic injury of the heart, *Am. Heart J.* **30**: 459-478, 1945.
4. Master, A. M.: Effect of injury and effort on the normal and the diseased heart, *New York State J. Med.* **46**: 2634, 1946.
5. Beck, C. S.: Contusion of the heart, *J. A. M. A.* **104**: 109, 1935.
6. Reed, L. K., and Berger, K. E.: Contusion of the heart, a case report, *Am. Heart J.* **30**: 622, 1945.
7. Moffat, C. F.: Contusion of the heart, *Canad. M. A. J.* **54**: 452, 1946.
8. White, P. D., and Smith, H. W.: Scientific proof in respect to injuries of the heart, *North Carolina Law Review* **24**: 1945-46.

EDITORIAL

COXSACKIE VIRUSES

THE term Coxsackie virus ("C virus") has been applied by Dalldorf¹ to a filtrable agent first obtained^{2,3} during the course of an epidemic of poliomyelitis in Coxsackie, N. Y., in 1948, by the injection into suckling mice of fecal extracts from two patients who presented the clinical picture of poliomyelitis. These same extracts did not produce poliomyelitis on intracerebral injection into monkeys. During the same season Dalldorf subsequently obtained a similar virus from nine other cases of "poliomyelitis" in New York, eight of which were not paralytic.

At the same time an extensive epidemic of poliomyelitis characterized by a very low mortality was in progress in Wilmington, Delaware. Dalldorf examined fecal specimens from 16 cases from this epidemic in which attempts to demonstrate poliomyelitis virus by injection into monkeys had failed, and he obtained C virus from five, three of which were from paralytic cases. Dalldorf⁴ has subsequently reviewed this work with C virus. Of 275 cases in all, adequately studied at the time of the report, strains of C virus were obtained from 27, of which 10 showed paralysis and 17 did not.

Infant mice are highly susceptible to infection by parenteral injections by any route. They may be infected by oral administration or intranasal instillation. In practice subcutaneous injections are satisfactory. The mice rapidly acquire resistance, and they can rarely be infected after the twelfth day. Suckling hamsters are also susceptible, but active infection has not been produced in any other species thus far tested.

Following oral administration or parenteral injection into *Cynomolgus* monkeys or chimpanzees, the animals acquire an inapparent infection with fever after four to nine days.^{5,6} They excrete virus in their pharyngeal secretions and feces for substantial periods and acquire specific neutralizing antibodies in the serum which persist at least six months. The virus does not cause poliomyelitis on intracerebral injection. The behavior of C virus is, therefore, the reverse of poliomyelitis virus which, as obtained from human sources, is pathogenic for monkeys but never for mice.

On the basis of the lesions produced in mice Dalldorf has distinguished two groups of C viruses. The more numerous group, A, two to 10 days

¹ Dalldorf, G.: The Coxsackie group of viruses, *Science* 110: 594, 1949.

² Dalldorf, G., and Sickles, G. M.: An unidentified filtrable agent isolated from the feces of children with paralysis, *Science* 108: 61-62, 1948.

³ Dalldorf, G., et al.: A virus recovered from the feces of "poliomyelitis" patients pathogenic for suckling mice, *J. Exper. Med.* 89: 567-582, 1949.

⁴ Dalldorf, G.: The Coxsackie viruses, *Bull. New York Acad. Med.* 26: 329-335, 1950.

⁵ Melnick, J. L., Shaw, E. W., and Curnen, E. C.: A virus isolated from patients diagnosed as nonparalytic poliomyelitis or aseptic meningitis, *Proc. Soc. Exper. Biol. and Med.* 71: 344-349, 1949.

⁶ Melnick, J. L., and Ledinko, N.: Infection of *Cynomolgus* monkeys with the Ohio type of Coxsackie virus (C virus), *J. Immunol.* 64: 101-110, 1950.

after inoculation causes a rapidly progressive flaccid paralysis typically involving all the skeletal muscles, but not the myocardium. The skeletal muscles show a diffuse and extreme degree of degeneration which, in animals which survive long enough, is followed by round cell infiltration and extensive proliferation of sarcolemma nuclei. These lesions are highly characteristic although not pathognomonic. Virus is present throughout the tissues and in the blood, but it is in maximum concentration in the muscles. Lesions of the central nervous system are trivial or absent, although virus is present in the brain.

In group B, the muscular degeneration was less extensive and usually focal, but severe degenerative necrotic lesions occurred in the brain, resulting in large areas of cystic degeneration. Such mice might live longer and show tremor, ataxia and spasticity rather than simple paralysis.

Biopsies of muscle in a few human cases have not shown definite lesions.

Serologically the strains in group B were found to be homogeneous and distinct from the group A strains, among which he found three distinct types. Several other serologically distinct types have since been demonstrated by other investigators (there are at least seven in all). In man as well as in experimental animals C viruses stimulate the production of neutralizing and complement fixing antibodies ^{7, 8, 9, 10} which are specific for the type and which have been utilized for diagnosis. All C viruses are distinct from poliomyelitis virus and the other important viruses with which they have been compared. Attempts to demonstrate interference between C viruses and the Lansing strain of poliomyelitis virus in mice have been unsuccessful.

Strains of C virus vary in virulence, and some mice may recover. Infant mice can be immunized passively through the milk ¹¹ and presumably through the blood by vaccinating the mothers during pregnancy.

The C viruses, like that of poliomyelitis, are among the smallest known, having a diameter of about 6 to 9 m μ as estimated from filtration and centrifugation tests.⁴ C virus is killed at 56° C., but it is relatively resistant outside the body and can be preserved for long periods in glycerine or in a frozen state. It resists the usual antibiotics and even precipitation by ammonium sulfate. It has been obtained from sewage from six cities in Connecticut and North Carolina, and from pools of flies from these states as well as from Ohio and Texas, both alone and in conjunction with polio-

⁷ Casals, J., et al.: Hemagglutination and complement fixation with Type I and II Albany strains of Coxsackie virus, *Proc. Soc. Exper. Biol. and Med.* **72**: 636-638, 1949.

⁸ Howitt, B. F., and Benefield, U. R.: Use of complement fixation in the differentiation of strains of Coxsackie virus, *Proc. Soc. Exper. Biol. and Med.* **73**: 90-92, 1950.

⁹ Findlay, G. M., and Howard, E. M.: Coxsackie viruses and Bornholm disease, *Brit. M. J.* **1**: 1233-1236, 1950.

¹⁰ Kraft, L. M., and Melnick, J. L.: Immunological reactions of the Coxsackie viruses. II. The complement fixation test, *J. Exper. Med.* **92**: 483-497, 1950.

¹¹ Melnick, J. L., Clarke, N. A., and Kraft, D. V. M.: Immunological reactions of the Coxsackie viruses. III. Cross-protection tests in infant mice born of vaccinated mothers. Transfer of immunity through the milk, *J. Exper. Med.* **92**: 499-505, 1950.

myelitis virus. One strain of C virus has been cultivated in media containing minced tissue from infant mice (Slater and Syverton), and one has been adapted to grow in the chick embryo (Huebner).

Reports confirming Dalldorf's observations have been published by a number of other investigators. Melnick et al.¹² in 1949 obtained C virus from three of 18 cases of nonparalytic illness in Ohio. From two of these, which had been diagnosed as "summer grippé," poliomyelitis virus had been previously isolated. In their earlier work they did not obtain C virus from paralyzed cases, but later they state¹³ that C virus, together with poliomyelitis virus, was obtained from four of a "number" of cases of poliomyelitis, three of which were paralytic. One of the cases yielding the virus presented the picture of severe epidemic pleurodynia.¹⁴

Howitt¹⁴ examined a large number of specimens, chiefly feces and oropharyngeal washings, which had originally been collected for the study of Newcastle disease virus and had been preserved frozen for periods up to two years. C virus was isolated from 97 cases from nine different states ranging from Delaware to Florida, Oklahoma and South Dakota. Virus was also isolated from the urine, blood, sputum and saliva, but never from the cerebrospinal fluid, although clinically pleocytosis has often been observed. It was obtained from 10 fatal cases; eight times from the brain and cord, twice from serum and once from nasopharyngeal washings. There was no assurance that the C virus was the cause of death in any of these cases. She also obtained virus from six of 12 healthy nurses (contacts), indicating that the virus is readily transmitted from person to person.

Huebner et al.¹⁵ studied a small epidemic of a mild febrile illness in Parkwood, Md., in 1949. He obtained C virus (Dalldorf's A, Type 2) from eight cases in five adjacent households. About three weeks later they made a survey of the entire community, examining 296 of 308 persons from 80 of the 84 households. C virus of the same type was obtained from all eight patients, from three contacts in the same households, and from five other scattered subjects. C virus of two other types was obtained from eight other persons in the community. Virus was excreted by the eight patients over periods of 9 to 76 days. Of 31 persons from whom virus was obtained at one time or another, none was severely ill and none showed a syndrome resembling poliomyelitis. Neither poliomyelitis nor meningitis occurred in the community during this period.

Much study has been devoted to the serological reactions in these cases. A detailed analysis is impracticable, but in brief, specific neutralizing anti-

¹² Melnick, J. L., et al.: Ohio strains of a virus pathogenic for infant mice (Coxsackie group). Simultaneous occurrence with poliomyelitis virus in patients with "summer grippé," *J. Exper. Med.* **91**: 185-195, 1950.

¹³ Curnen, E. C., Shaw, E. W., and Melnick, J. L.: Disease resembling poliomyelitis associated with a virus pathogenic for infant mice, *J. A. M. A.* **141**: 894-901, 1950.

¹⁴ Howitt, B. F.: Recovery of the Coxsackie group of viruses from human sources, *Proc. Soc. Exper. Biol. and Med.* **73**: 443-448, 1950.

¹⁵ Huebner, R. J., et al.: Studies of Coxsackie viruses, *J. A. M. A.* **144**: 609-612, 1950.

bodies and (perhaps a little less consistently) complement fixing antibodies have demonstrated in substantially all cases adequately examined during the convalescent phase. This activity was exerted on the serological type of virus isolated from the subject, rarely also on some other type. In many cases, however, serum obtained during the acute phase of the infection, even as early as the fifth day, showed similar activity. In some cases in which the serum from the acute phase showed neutralizing power, careful titrations are reported to have shown a specific increase in the convalescent serum. It has since been shown, in cases in which the date of onset was precisely known, that antibodies may be demonstrable as early as the second or third day.

In a considerable number of cases, serum from healthy subjects has shown similar activity. Thus in Huebner's study of the community in Parkton, Md., 77.4 per cent of 158 subjects tested showed neutralizing power. In a group of over 200 children in Winston-Salem, North Carolina, reported by Melnick and Ledinko¹⁶ from a community in which the virus had been demonstrated, 80 per cent of those 7 years of age and older showed neutralizing antibodies in the serum.

A possible source of serious technical error in such tests has recently been pointed out by Howitt¹⁷ and by Ginsberg and Horsfall.¹⁸ It was found that the neutralizing power of many normal human sera and of some normal animal sera for Newcastle disease virus,^{17, 18} for influenza A and B viruses and for mumps virus¹⁸ was not due to specific antibodies but to a nonspecific thermolabile constituent which deteriorated quickly on standing unless frozen.* This resembles complement in many ways but apparently is not identical with it. In the case of the Cocksackie viruses, however, that this is not a source of error has been shown by the work of Melnick and Ledinko¹⁶ who demonstrated that the active substances are thermostable at 56° C., are specific and retain their activity for long periods at ordinary ice box temperatures.

Assuming adequate technic, the presence of such specific antibodies constitutes strong evidence of previous contact with the virus with presumably a subclinical infection. Manifestly, however, this has little or no diagnostic value as far as a current illness is concerned unless a specific rise in titer during the illness can be unequivocally demonstrated. To accomplish this, the first specimen of blood should be secured at the very onset of the disease.

¹⁶ Melnick, J. L., and Ledinko, N.: Immunological reactions of the Cocksackie viruses. I. The neutralization test: Technic and application, *J. Exper. Med.* **92**: 463-482, 1950.

¹⁷ Howitt, B. F.: A nonspecific heat-labile factor in the serum neutralization test for Newcastle disease virus, *J. Immunol.* **64**: 73-84, 1950.

¹⁸ Ginsburg, H. S., and Horsfall, F. R., Jr.: A labile component of normal serum which combines with various viruses. Neutralization of infectivity and inhibition of hemagglutination by the component, *J. Exper. Med.* **90**: 475-496, 1950.

* The principal evidence on which was based the claim that Newcastle disease virus can infect man is therefore invalid. This may well be true of some surprising instances of supposed subclinical infection with other agents, such as Japanese type B encephalitis in this country.

Even then concurrent infection with poliomyelitis virus or some other agent must be excluded.

The most conclusive evidence that Coxsackie virus can cause disease in man is furnished by accidental infections in the laboratory, six cases of which have been reported by Shaw, Melnick and Curnen.¹⁹ In three cases infection followed pipetting infectious material into the mouth, in two others wiping up such material which had been spilled on the floor. In all six, the corresponding type of virus was obtained from the feces, throat swabs or both. Three different types of virus were involved. In all cases antibodies for the corresponding type developed during convalescence.

The incubation period ranged from three to five days. In five cases the illness was mild, with fever for a few days, headache, malaise, weakness, nausea and most characteristically dull aching pain in the chest of moderate severity. In one case these pains were severe, there was stiffness of the neck, hyperesthesia and a pleocytosis (375 cells) in the cerebrospinal fluid. The leukocyte count was not significantly altered. There was no paralysis or sequela.

Findlay and Howard⁹ observed similar symptoms in a volunteer infected by intranasal inoculation of C virus (Type 2). After an incubation period of 46 hours the subject had a mild illness of three days' duration with slight fever and pain in the chest below the right scapula, radiating anteriorly in the intercostal spaces and aggravated by deep breathing or laughing. The complement fixation reaction was negative at the time of inoculation but became positive on the third day of illness. They also reported a few cases of laboratory infection, the diagnosis being based on positive complement fixation reactions.

Curnen²⁰ has recently reviewed the clinical symptoms of 14 cases "considered to represent examples of infection by C viruses." Virus was isolated from all and serological reactions obtained in 12. He differentiates three clinical types of illness. (1) One resembling nonparalytic poliomyelitis. In these five cases headache, pain and stiffness in the neck and back and nausea and vomiting were prominent. Pleocytosis in the cerebrospinal fluid was found in the two cases examined. (2) One resembling epidemic pleurodynia. In these five cases, one sporadic and four in laboratory workers, the characteristic feature was pain of some severity in the muscles of the lower part of the thorax, occasionally in the epigastrium, aggravated by deep breathing, laughing or coughing. (3) A nondescript febrile infection in four cases, "summer gripe," with malaise and general aching of nonspecific character. In two of these poliomyelitis virus had previously been demonstrated by Sabin and Steigman.

¹⁹ Shaw, E. W., Melnick, J. L., and Curnen, E. C.: Infection of laboratory workers with Coxsackie virus, *Ann. Int. Med.* 33: 32-40, 1950.

²⁰ Curnen, E. C.: Human disease associated with the Coxsackie viruses, *Bull. New York Acad. Med.* 26: 335-342, 1950.

In either of the last two groups there may also be manifestations of meningeal irritation and pleocytosis of the cerebrospinal fluid, "aseptic meningitis."

Coxsackie virus has been isolated from both paralytic and nonparalytic cases of "poliomyelitis." In some cases it has been found with poliomyelitis virus,^{21, 22} although usually the latter virus could not be demonstrated. The pathogenic significance of the C virus in these cases is open to serious question, particularly in the paralytic cases. That C virus may be significant in some of the nonparalytic cases is suggested by the epidemiological observations of Curnen.²⁰ Although in New England, New York and Delaware many cases of C virus infection have been demonstrated in communities in which poliomyelitis was prevalent, there were distinct differences in the incidence of paralytic and nonparalytic cases. The latter were more nearly restricted to children, and the peak of their incidence occurred in August, whereas that of the paralytic cases was in September and October. The relation of the C viruses to poliomyelitis virus and to the nonparalytic cases of "poliomyelitis" is still an unsolved problem.

Armstrong et al.²² demonstrated C virus in a child with the Guillain-Barré-Landry syndrome. There was extensive ascending paralysis with transient dysphagia but rapid recovery.

That C viruses may be causally related to epidemic pleurodynia receives considerable support from the observations of Findlay and Howard⁹ in London. They isolated a C virus (Type 2) from the blood, feces and nasal washings of a typical case of "Bornholm disease" (epidemic pleurodynia) on the third day of illness, when complement fixing antibodies were also present. Symptoms typical of a mild attack of this disease occurred in the volunteer who had been inoculated intranasally with the virus.

They demonstrated positive complement fixation reactions with Type 2 C virus in all of 18 cases with a history of recent attacks of Bornholm disease from three separate areas in England in which epidemics had occurred, including one who contracted his illness in Aden. They also obtained positive reactions to the same virus in 14 of 15 individuals who had had an illness characterized by muscular pain of the type described but in whom the diagnosis had not been made clinically. The British observers²³ have emphasized the frequency with which pain is referred to the tip of the shoulder and suggest that this and the pain and tenderness often present in the upper abdomen may be due to involvement of the diaphragm. In all these cases, negative reactions were obtained with Type 1 virus.

Positive reactions with Type 1 virus, however, were obtained with serum of several cases of Bornholm disease from other districts in England

²¹ Melnick, J. L.: Studies on Coxsackie virus: Properties, immunological aspects and distribution in nature, *Bull. New York Acad. Med.* 26: 342-356, 1950.

²² Armstrong, M. P., et al.: Studies on poliomyelitis in Ontario. II. Isolation of the Coxsackie virus in association with poliomyelitis virus: a preliminary report, *Canad. J. Pub. Health* 41: 51-59, 1950.

²³ Hopkins, J. H. S.: Bornholm disease, *Brit. M. J.* 1: 1230-1232, 1950.

and of one case from Versailles, France. Specific antibodies for several types of C virus have also been demonstrated by others in sera from Denmark and Sweden.

Coxsackie viruses are, therefore, widely distributed both in North America and in northern Europe. From the epidemiological standpoint they resemble poliomyelitis virus in their seasonal incidence and mode of dissemination, being passed readily from one person to another by direct contact and presumably by fecal contamination. They undoubtedly may cause disease in man, predominantly in young children: usually a mild infection which may appear clinically as an influenza-like illness; as epidemic pleurodynia, or "aseptic meningitis." As in the case of poliomyelitis, unrecognized or subclinical infections are extremely common if the serological reactions can be trusted, and they apparently may involve at least 80 per cent of the population in communities in which the virus becomes disseminated. Coxsackie viruses have been found repeatedly in close association with poliomyelitis virus during epidemics of the latter disease, but their pathogenicity here is doubtful. It is quite possible that they may be the cause of illness at least in some cases diagnosed as nonparalytic poliomyelitis. Their relation to poliomyelitis is a fascinating problem that still awaits solution.

P. W. C.

REVIEWS

Hormone Assay. By C. W. EMMENS, Editor, Department of Veterinary Physiology, University of Sydney, Sydney, Australia. 556 pages; 23.5 × 15.5 cm. Academic Press, Inc., N. Y. 1950. Price, \$10.00.

This is a much needed summary of both biological and chemical methods of hormone assay. The principal factors of the pituitary, thyroid, parathyroid, adrenal, pancreas and gonads are included. The gastrointestinal group of hormones is not included although one might consider that secretin, at least, would deserve a place in a volume as inclusive as this. Chapters have been prepared by workers whose original contributions to the particular fields have been outstanding in recent years. The contributors have, where practicable, made valuable comparative evaluations of the various procedures. Some of the best established methods are presented in detail, but of a larger number which are less standard only principles or main details are presented. Some of these less established procedures provide a key to probable future trends. The references enable the reader to pursue further the subjects concerning which he may desire more details.

The volume is of particular value to individuals supervising or working in laboratories doing endocrine assays. It is also a useful reference book for the clinician, particularly the endocrinologist who may wish to achieve more understanding of the technical background of assay results.

GORDON E. GIBBS, M.D.

Differential Diagnosis of Chest Diseases. By J. J. SINGER, M.D., F.A.C.P., F.C.C.P. 344 pages; 15.5 × 24 cm. Lea and Febiger, Philadelphia. 1949. Price, \$7.50.

This book is designed to give a "balanced and inclusive view of the common abnormalities encountered in the examination of the chest." It is divided into six sections—Diagnostic Methods, Thoracic Cage, Diseases of the Pleura, Mediastinum, Diaphragm, and Tracheo-Bronchial Tree and Lungs. Each major thoracic abnormality is dealt with systematically, with emphasis on etiology and pathology, and with especial attention directed to differential diagnosis. As the author says, the most important attack on disease is correct diagnosis, and treatment itself is beyond the scope of this small volume.

The content of the book is obviously based on the author's wide experience and well balanced outlook, and will serve as a concise but adequate work of reference for the vast majority of chest diseases encountered in practice. Diseases which are not of the chest but which will enter into the differential diagnosis of chest symptoms—cervical rib, diaphragmatic hernia, subphrenic abscess—are also given full treatment. The text is abundantly illustrated with a total of 171 excellent x-ray photographs and diagrams.

"In style, the aim has been for conciseness. . . . In rhetoric, I have sought simplicity." Dr. Singer has achieved a commendably crisp and simple style, but one feels in places that some amplification would make the text more easily understood and therefore even more valuable.

Again, despite his prefatory homily on semantics, the author falls into one or two common linguistic traps: thus he uses "predicates" where he means "pre-disposes," "mitigate against" for "militate against," and "apt" persistently where "likely" is the better word.

Such criticisms are obviously trivial, and are not intended to detract from the value and high standard of the book in general. There is a wealth of information

in these pages, and an ample bibliography for the interested deliver. All in all the general practitioner, for whom this volume is primarily intended, should find Dr. Singer's easily read text of great value.

H. J. L. M.

Immortal Magyar: Semmelweis, Conqueror of Childbed Fever. By FRANK G. SLAUGHTER, M.D. 211 pages; 14.5 × 21.5 cm. Henry Schuman, New York. 1950. Price, \$3.50.

This short and easy to read treatise is a biography of "Semmelweis, Conqueror of Childbed Fever." The subject is treated critically and objectively by the author. Semmelweis's unusual life is portrayed without embellishments and fictional additions.

Stress is placed on the importance of Semmelweis's contribution, not only to obstetrics, but also to surgery and gynecology, in which he practised his theories constantly. His influence on Lister is emphasized by Slaughter on several occasions.

The biography contains sufficient quotations from various sources of material on the life of Semmelweis, yet these are few enough not to encroach upon the fluent style of the author's easy way of writing. Two hours spent reading this book will be well rewarded.

D. F. K.

Clinical Electrocardiography. By FRANCIS F. ROSENBAUM, M.D., Assistant Clinical Professor of Medicine, Marquette University School of Medicine, etc. Reprinted from Oxford Loose-Leaf Medicine, Henry A. Christian, M.D., Editor. Oxford University Press, New York. 1950. Pages 370 (1) to 370 (52-149). Price, \$4.50.

This small volume contains much interesting information concerning the electrocardiogram, and seems calculated to impress the reader with the limitations as well as with the many applications of this diagnostic method. The text is well written and the material is clearly presented and adequately illustrated.

This book would seem suitable particularly for the physician who seeks a better understanding of the clinical aspects of electrocardiography, and who must rely upon others for the original interpretations. For him, this text is heartily recommended as a basic orientation course.

S. S.

Malignant Disease and Its Treatment by Radium. Vol. III. 2nd Ed. By SIR STANFORD CADE, K.B.E., C.B., F.R.C.S., M.R.C.P., Surgeon, Westminster Hospital; Consulting Surgeon, Mount Vernon Hospital and Radium Institute; with a foreword by SIR ERNEST ROCK CARLING, F.R.C.P., F.F.R., Consulting Surgeon and Vice-President, Westminster Hospital. 446 pages; 15.5 × 23.5 cm. The Williams and Wilkins Co., Baltimore. 1950. Price, \$12.50.

This is the second of the volumes dealing with the clinical aspects of malignancy. Although one might, from the title, expect a discussion of a single phase of therapy of malignancy this is definitely not the case. Throughout this comprehensive work the author draws upon his broad surgical experience to give us a truly objective basis for the handling of malignant disease. For each clinical stage of a particular malignancy we are given the results of treatment by surgery, irradiation, or a combination of both. The author draws on his extensive work and that of others in reaching a decision on the best method of treatment.

Should irradiation be preferable, Sir Stanford goes into great detail in describing his method of therapy. After reading his instructions one can readily appreciate

the time and patience required to get good results with radium, and also why our English cousins surpass us in this mode of therapy.

The clinician will find this volume easy to read and of great use for many years. The chapters are so arranged that one may obtain a good review of the natural history, gross, and microscopic pathology, clinical stages, prognosis, and a discussion of the best method of treatment without wading through a mass of technical detail. The radiologist interested in radium therapy will find this a valuable addition to his library.

The volume is well illustrated with black and white and color plates.

A. G. S.

BOOKS RECEIVED

Books received during November are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Basic Principles of Clinical Electrocardiography. By HANS H. HECHT, M.D., Associate Professor of Medicine, University of Utah School of Medicine. 88 pages; 22 × 14 cm. (limp leather binding). 1950. Charles C. Thomas, Publisher, Springfield, Illinois. Price, \$2.00.

Sir Thomas Browne: A Doctor's Life of Science and Faith. By JEREMIAH S. FINCH, Assistant Dean of the College, Princeton University. 319 pages; 21.5 × 14.5 cm. 1950. Henry Schuman, New York. Price, \$3.50.

The Burden of Diseases in the United States. By ALFRED E. COHN, Member Emeritus, The Rockefeller Institute for Medical Research; and CLAIRE LINGG, Secretary, Former Committee on Research, New York Heart Association. 129 pages, with separate portfolio containing colored charts; 31 × 23.5 cm. 1950. Oxford University Press, New York. Price, \$10.00.

Cybernetics: Circular Causal, and Feedback Mechanisms in Biological and Social Systems. Transactions of the Sixty Conference, March 24-25, 1949, New York, N. Y. Edited by HEINZ VON FOERSTER, Department of Electrical Engineering, University of Illinois. 209 pages; 23 × 15 cm. (paper-bound). 1950. Josiah Macy, Jr. Foundation, New York. Price, \$3.50.

Die Hemmkörperhämophilie. By DR. ERWIN DEUTSCH. 112 pages; 24 × 16 cm. (paper-bound). 1950. Springer-Verlag, Vienna. Price, \$3.90.

Heparin und Heparinoide Dicumarol. Möglichkeiten und Ergebnisse einer thrombotischen und thrombolytischen Therapie. By TH. HALSE. 225 pages; 22.5 × 15 cm. 1950. S. Hirzel Verlag, Zurich. Price, Ganzleinen Fr. 13.50.

Hormone Assay. Edited by C. W. EMMENS, Department of Veterinary Physiology, University of Sydney, Sydney, Australia. 556 pages; 23.5 × 15.5 cm. 1950. Academic Press, Inc., New York. Price, \$10.00.

Kallikrein Padutin. By DR. MED. EMIL K. FREY, DR. PHIL. HEINRICH KRAUT, and DR. PHIL., DR. MED. EUGEN WERLE. 209 pages; 24.5 × 16.5 cm. 1950. Ferdinand Enke Verlag, Stuttgart. Price, geheftet DM 17.80; gebunden DM 20.—

Lehrbuch der inneren Medizin. By M. BROGLIE, Neumünster/Schleswig; H. DENNIG, Stuttgart; K. HANSEN and W. GRONEMEYER, Lübeck; N. HENNING, Würzburg; A. HEYMER, Essen; H. REINWEIN, Kiel; F. SCHELLONG, Münster; C. SCHALTEN-

- BRAND, Würzburg, and H. SCHULTEN, Köln. 1,117 pages; 24.5 × 18 cm. 1950. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, New York. Price, Ganzleinen DM 39.—
- The Medical Annual—1950—A Year Book of Treatment and Practitioners' Index—68th Year.* Editors: SIR HENRY TIDY, K.B.E., M.A., M.D. (Oxon), F.R.C.P., and A. RENDLE SHORT, M.D., B.S., B.S.C., F.R.C.S. 439 pages; 22 × 14.5 cm. 1950. The Williams & Wilkins Company, Baltimore. Price, \$5.50.
- The Neurologic Examination, Incorporating the Fundamentals of Neuroanatomy and Neurophysiology.* By RUSSELL N. DEJONG, M.D., Professor of Neurology and Chairman of the Department of Neurology, University of Michigan Medical School. 1,079 pages; 26 × 18 cm. 1950. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, \$15.00.
- Physicians Federal Income Tax Guide and Simplified Accounting Record—1951 Edition—for the Preparation of 1950 Returns and 1951 Estimates.* By HUGH J. CAMPBELL and JAMES B. LIBERMAN. 127 pages; 28 × 21 cm. (paper-bound) 1950. Doniger & Raughley, Inc., Great Neck, New York. Price, \$2.50.
- Physiologie und Pathologie des Bilirubinstoffwechsels als Grundlagen der Ikterusforschung.* By DR. MED. ET PHIL. HABIL. TR. BAUMGÄRTEL. 271 pages; 25 × 17.5 cm. 1950. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune and Stratton, New York. Price, Ganzleinen DM 27.—
- Problems of Infancy and Childhood. Transactions of the Third Conference, March 7-8, 1949, New York, N. Y.* Edited by MILTON J. E. SENN, M.D., Departments of Pediatrics and Psychiatry, Yale University School of Medicine. 156 pages; 23 × 15 cm. (paper-bound). 1949. Josiah Macy, Jr. Foundation, New York. Price, \$1.25.
- Renal Function. Transactions of the First Conference, October 20-21, 1949, New York, N. Y.* Edited by STANLEY E. BRADLEY, Department of Medicine, College of Physicians & Surgeons, Columbia University. 172 pages; 23.5 × 15.5 cm. 1950. Josiah Macy, Jr. Foundation, New York. Price, \$2.50.
- Therapeutics in Internal Medicine.* Edited by FRANKLIN A. KYSER, M.D., M.S., F.A.C.P., Associate in Medicine, Northwestern University Medical School, Chicago, etc. 715 pages; 25.5 × 17.5 cm. 1950. Thomas Nelson & Sons, New York. Price, \$12.00.
- Twentieth Century Mental Hygiene: New Directions in Mental Health.* By MAURICE J. SHORE et al. 444 pages; 22.5 × 14 cm. 1950. Social Sciences Publishers, New York. Price, \$6.00.

COLLEGE NEWS NOTES

CONVENTION NUMBER—ANNALS OF INTERNAL MEDICINE

The February, 1951, issue of the ANNALS OF INTERNAL MEDICINE will be the Convention Number. In addition to the usual scientific articles, this issue will contain the complete program of the 32nd Annual Session of the American College of Physicians which will be held in the Kiel Auditorium in St. Louis, Mo., April 9-13, 1951.

The following Fellows of the College have become Life Members since the publication of the last issue of the ANNALS:

Dr. Samuel Simkins, Philadelphia, Pa.
Dr. Sidney Davidson, Lake Worth, Fla.
Dr. Leslie G. Kindschi, Monroe, Wis.

The College Life Membership Plan is an equitable and practicable arrangement by which a member may pay his dues during the productive years and while his income is greatest, thus avoiding the burden of dues later in life. Life Membership offers security in advancing years against misfortune which often necessitates relinquishment of one's most cherished professional memberships because of the burden of dues.

The Life Membership fee entitles each Fellow or Master to permanent privileges of membership, to the benefits of the Annual and Regional Sessions, to the ANNALS OF INTERNAL MEDICINE, etc. Each Life Member receives a framed certificate and his name is inscribed in the Life Membership Roll at the College. Life Members are active members for life. All Life Membership fees are deposited in the permanent Endowment Fund of the College and thus contribute to the security of the College as well as to the security of its members. The Life Membership fee is deductible on Federal income tax returns.

A.C.P. POSTGRADUATE COURSES, SPRING OF 1951

The following Postgraduate Courses will appear on our program for the Spring of 1951:

PHYSIOLOGICAL APPROACH TO CLINICAL PROBLEMS IN THE CARDIOVASCULAR DISEASES: George C. Griffith, M.D., F.A.C.P., Director; University of Southern California School of Medicine, Los Angeles, Calif.; February 12-17, 1951. Fees: A.C.P. Members, \$30.00; Non-members, \$60.00.

RECENT PROGRESS IN INTERNAL MEDICINE: Howard P. Lewis, M.D., F.A.C.P., Director; University of Oregon Medical School, Portland, Ore.; March 19-23, 1951. Fees: A.C.P. Members, \$30.00; Non-members, \$60.00.

ELECTROCARDIOGRAPHY: Gordon B. Myers, M.D., F.A.C.P., Director; Wayne University College of Medicine, Detroit, Mich.; March 26-31, 1951. Fees: A.C.P. Members, \$30.00; Non-members, \$60.00.

SOME RECENT DEVELOPMENTS IN THE PRINCIPLES AND PRACTICE OF MODERN INTERNAL MEDICINE: Garfield G. Duncan, M.D., F.A.C.P., Director; Pennsylvania Hospital, Philadelphia, Pa.; May 7-11, 1951. Fees: A.C.P. Members, \$30.00; Non-members, \$60.00.

ELECTROCARDIOGRAPHY: BASIC PRINCIPLES AND INTERPRETATION: Conger Williams, M.D., Director; Massachusetts General Hospital, Boston, Mass.; May 14-19, 1951. Fees: A.C.P. Members, \$60.00; Non-members, \$120.00.

DYNAMIC THERAPEUTICS IN CHRONIC DISEASES: Howard A. Rusk, M.D., F.A.C.P., Director; New York University-Bellevue and Goldwater Hospitals, New York, N. Y.; May 21-25, 1951. Fees: A.C.P. Members, \$30.00; Non-members, \$60.00.

DISEASES DUE TO IMMUNE MECHANISMS: Leo H. Crip, M.D., Director; University of Pittsburgh School of Medicine, Pittsburgh, Pa.; one week, date to be announced. Fees: A.C.P. Members, \$30.00; Non-members, \$60.00.

INTERNAL MEDICINE: Chester S. Keefer, M.D., F.A.C.P., Director; Boston University School of Medicine and Massachusetts Memorial Hospitals, Boston, Mass.; one week, date to be announced. Fees: A.C.P. Members, \$30.00; Non-members, \$60.00.

The Postgraduate Bulletin will be published early in January and all members of the College will receive a copy.

COURSE NO. 1—PHYSIOLOGIC APPROACH TO CLINICAL PROBLEMS IN CARDIOVASCULAR DISEASES

(February 12-17, 1951)

THE UNIVERSITY OF SOUTHERN CALIFORNIA SCHOOL OF MEDICINE

LOS ANGELES COUNTY HOSPITAL AUDITORIUM

George C. Griffith, M.D., F.A.C.P., *Director*

(Minimal Registration, 50;
Maximal Registration, 125)

Fees: A.C.P. Members, \$30.00
Non-members, \$60.00

Consulting Committee

B. O. RAULSTON, M.D., F.A.C.P.
PAUL STARR, M.D., F.A.C.P.
EGERTON CRISPIN, M.D., F.A.C.P.
LELAND HAWKINS, M.D., F.A.C.P.
JOHN JONES, M.D.
SEELEY G. MUDD, M.D., F.A.C.P.
W. HARRY MULLER, M.D.
ROY C. THOMAS, M.D., F.A.C.P.
WILLIAM P. THOMPSON, M.D.

OFFICERS OF INSTRUCTION

(All members of the faculty are from the University of Southern California School of Medicine, unless otherwise indicated.)

LEWIS T. BULLOCK, M.D., Assistant Clinical Professor of Medicine.
ROBERT R. COMMONS, M.D., Instructor in Medicine.

RICHARD S. COSBY, M.D., F.A.C.P., Assistant Clinical Professor of Medicine.
 FREMONT E. DAVIS, M.D., Instructor in Pathology.
 J. N. DELAMATER, M.D., Professor of Medicine and Associate Dean.
 HARRY J. DEUEL, Ph.D., Professor of Biochemistry.
 SIM P. DIMITROFF, M.D., Instructor in Medicine.
 DOUGLAS R. DRURY, M.D., Professor of Physiology.
 DONALD T. EDMEADES, M.D., F.A.C.P., Assistant Clinical Professor of Medicine.
 HUGH A. EDMONDSON, M.D., Professor of Pathology.
 STEPHEN R. ELEK, M.D., F.A.C.P., Instructor in Medicine.
 H. RUSSELL FISHER, M.D., F.A.C.P., Professor of Pathology.
 JACK FLASHER, M.D., Assistant Professor of Medicine.
 ALVIN G. FOORD, M.D., F.A.C.P., Professor of Pathology.
 ERNEST GEIGER, Ph.D., Professor of Pharmacology and Toxicology.
 HARRY GOLDBLATT, M.D., Professor of Pathology.
 GEORGE C. GRIFFITH, M.D., F.A.C.P., Professor of Medicine.
 ERNEST M. HALL, M.D., F.A.C.P., Professor of Pathology.
 ARTHUR M. HOFFMAN, M.D., F.A.C.P., Associate Clinical Professor of Medicine.
 GEORGE JACOBSON, M.D., Assistant Professor of Medicine (Radiology).
 JULIUS KAHN, M.D., Associate Clinical Professor of Medicine.
 DAVID C. LEVINSON, M.D., Instructor in Medicine.
 LOUIS E. MARTIN, M.D., F.A.C.P., Associate Clinical Professor of Medicine.
 VERNE R. MASON, M.D., Clinical Professor of Medicine.
 EDGAR F. MAUER, M.D., Assistant Clinical Professor of Medicine.
 HAROLD MILLER, M.D., Research Fellow in Medicine.
 W. HARRY MULLER, M.D., Assistant Professor of Surgery, University of California Medical School at Los Angeles.
 BERTRAM M. MYERS, M.D., Instructor in Surgery.
 MORRIS H. NATHANSON, M.D., F.A.C.P., Associate Clinical Professor of Medicine.
 DONALD W. PETIT, M.D., Assistant Professor of Medicine.
 MYRON PRINZMETAL, M.D., Associate Clinical Professor of Medicine, University of California Medical School, Berkeley, Calif.
 EDWARD C. ROSENOW, JR., M.D., F.A.C.P., Associate Professor of Medicine.
 EDWARD SHAPIRO, M.D., Assistant Clinical Professor of Medicine.
 JACK A. SHEINKOPF, M.D., Assistant Clinical Professor of Medicine.
 PAUL STARR, M.D., F.A.C.P., Professor of Medicine.
 ROBERT STRAGNELL, M.D., Fellow in Medicine.
 MARCY SUSSMAN, M.D., Professor of Medicine (Radiology).
 WILLIAM P. THOMPSON, M.D., Clinical Professor of Medicine, College of Medical Evangelists.
 MEYER C. THORNER, M.D., Instructor in Medicine.
 ARNOLD G. WARE, Ph.D., Assistant Professor of Biochemistry and Nutrition.
 LAWRENCE A. WILLIAMS, M.D., F.A.C.P., Associate Clinical Professor of Medicine.
 TRAVIS W. WINSOR, M.D., F.A.C.P., Assistant Clinical Professor of Medicine.
 WILLARD J. ZINN, M.D., Assistant Clinical Professor of Medicine.

This course is arranged for physicians who are interested in both the physiology and clinical aspects of heart disease. Each day is so planned that the morning hours will be given over to a definite subject with progressive steps in the study of the various phases of that general subject.

The afternoon will continue with the same subject starting out with an unknown Clinical Pathological Conference and a study of cases on the wards of the Los Angeles County Hospital. Much of the material for these presentations will be drawn from the Cardiovascular Laboratory and from the very large number of patients available in the Los Angeles County Hospital.

The newer work on the hemodynamics and physiology of the pulmonary circulation, the physiology of the operable congenital heart lesions, as well as the physiology of congestive failure, will be stressed. Ample opportunity will be given for round table discussions.

Hotel Accommodations: Accommodations may be obtained at the Biltmore and Alexandria Hotels in Los Angeles, or at the Huntington or Green Hotels in Pasadena. Identify yourself with this course when applying for hotel reservations.

Transportation: Taxi and bus service to the Hospital is readily available. Luncheon may be obtained in the hospital cafeteria.

Notebooks containing outlines of the lectures and ample space for taking notes will be provided.

OUTLINE OF COURSE

Monday, February 12

A.M. Session

- 9:00 Registration.
9:30 Welcome.
DEAN B. O. RAULSTON, M.D., F.A.C.P.
9:45 PHOEBUS BERMAN, M.D., Medical Director, Los Angeles County Hospital.
10:00-10:30 The Embryology and Anatomy of the Heart in Relation to Congenital Heart Disease.
DR. SHEINKOPF.
10:30-11:00 Clinical Recognition of Congenital Heart Disease.
DR. GRIFFITH.
11:00-11:20 History, Purpose and Technic of Cardiac Catheterization.
DR. LEVINSON.
11:20-11:40 Cyanosis in Congenital Heart Disease.
DR. COSBY.
11:40-12:00 Angiocardiography in Congenital Heart Disease.
DR. ZINN.

P.M. Session

- 1:30- 2:30 Clinical Pathological Conference.
DR. THOMPSON, Cardiologist.
DR. HALL, Pathologist.
2:30- 5:00 Case Studies in Congenital Heart Disease:
1. Transportation of the Pulmonary Veins.
DR. LEVINSON.
2. Interatrial Septal Defect.
DR. GRIFFITH.
3. Interventricular Septal Defect.
DRS. COSBY AND JACOBSON.
4. Pulmonary Stenosis.
DRS. ZINN, JACOBSON AND MULLER.
5. Patent Ductus Arteriosus.
DRS. LEVINSON, JACOBSON AND MYERS.
6. Coarctation of Aorta.
DRS. GRIFFITH, JACOBSON AND MYERS.
7. Tetralogy of Fallot.
DRS. COSBY, JACOBSON AND MYERS.

8. Tetralogy of Eisenmenger.

DRS. ZINN, JACOBSON AND MYERS.

9. Summary.

DR. GRIFFITH.

Tuesday, February 13

A.M. Session

9:00- 9:30 Rôle of the Streptococci in Rheumatic Fever.

DR. DELAMATER.

9:30- 9:45 Incidence and Geographical Distribution.

DR. DIMITROFF.

9:45-10:15 Pathogenesis of Rheumatic Fever.

DR. GRIFFITH.

10:15-10:45 Types of Rheumatic Fever.

DR. MARTIN.

10:45-11:15 Differential Diagnosis of Rheumatic Fever.

DR. GRIFFITH.

11:15-12:00 Treatment of Rheumatic Fever, Including ACTH.

DR. SHEINKOPF.

P.M. Session

1:30- 2:30 Clinical Pathological Conference.

DRS. MASON AND FISHER.

2:30- 5:00 *Wards Rounds:*

Group I—Ward 7000.

DR. GRIFFITH.

Group II—Ward 7200.

DR. PETIT.

Group III—Ward 7400.

DR. COMMONS.

Group IV—Ward 7600.

DR. HOFFMAN.

Group V—Ward 7700.

DR. KAHN.

Group VI—Ward 7800.

DR. EDMEADES.

Wednesday, February 14

A.M. Session

9:00- 9:20 Management of the Arrhythmias.

DR. ELEK.

9:20- 9:40 New Drugs in Management of Arrhythmias.

DRS. NATHANSON AND MILLER.

9:40-10:00 Management of Syphilitic Heart Disease.

DR. THORNER.

10:00-10:30 Management of Heart Failure.

DR. GRIFFITH.

10:30-11:00 Preventive Treatment of Coronary Occlusion.

DR. THOMPSON.

11:00-12:00 Medical Therapy in Peripheral Vascular Disease.

DR. FLASHER.

P.M. Session

- 1:30- 2:30 Clinical Pathological Conference.
DRS. ROSENOW AND EDMONDSON.
- 2:30- 3:30 Physiological Aspects and Surgical Treatment of Mitral Stenosis.
Panel Discussion.
DRS. GRIFFITH, LEVINSON, COSBY, ZINN AND MULLER.
- 3:30- 4:00 Cardiovascular Roentgenology.
DR. SUSSMAN.
- 6:30 Reception and Dinner for members and their wives at the California Club.

Thursday, February 15

A.M. Session

- 9:00-10:00 Humoral Mechanisms of Hypertension.
DR. GOLDBLATT.
- 10:00-10:30 Early Renal Lesions Predisposing to Hypertension.
DR. COMMONS.
- 10:30-11:00 Experimental Hypertension.
DR. DRURY.
- 11:00-12:00 Clinical Electrocardiographic and Pathologic Conference.
DRS. THOMPSON AND STAFF.

P.M. Session

- 1:30- 2:30 Clinical Pathological Conference.
DRS. HOFFMAN AND DAVIS.
- 2:30- 3:00 Pathogenesis of Coronary Artery Disease.
DR. EDMEADES.
- 3:00- 3:30 Experimental Studies in Fat Metabolism.
DR. DEUEL.
- 3:30- 4:15 Cholesterol.
DR. GEIGER.
- 4:15- 5:00 Significance of Blood Colloids in Arteriosclerosis.
DR. ZINN.

Friday, February 16

A.M. Session

- 9:00- 9:45 Studies in Blood Coagulation.
DR. WARE.
- 9:45-10:00 Prothrombin Time Determination.
DR. STRAGNELL.
- 10:00-10:45 Anticoagulant Therapy in Cardiovascular Diseases.
DR. LEVINSON.
- 10:45-11:15 Treatment of Coronary Artery Disease.
DR. GRIFFITH.
- 11:15-12:00 Metabolic Approach to Cardiovascular Disease.
DR. STARR.

P.M. Session

- 1:30- 2:30 Clinical Pathological Conference.
DRS. BULLOCK AND FOORD.
- 2:30- 5:00 *Ward Rounds:*
Group I—Ward 7000.
DR. GRIFFITH.

Group II—Ward 7200.

DR. STARR.

Group III—Ward 7400.

DR. WILLIAMS.

Group IV—Ward 7600.

DR. SHAPIRO.

Group V—Ward 7700.

DR. ROSENOW.

Group VI—

DR. MAUER.

Saturday, February 17

A.M. Session

9:00-10:00 Unipolar Electrocardiography.

DR. WINSOR.

10:00-10:20 Back Leads in Post Myocardial Infarction.

DR. ELEK.

10:20-11:00 Electrographic Diagnosis.

DR. COSBY.

11:00-12:00 Auricular Arrhythmias.

DR. PRINZMETAL.

A.C.P. REGIONAL MEETINGS, 1951

The following regional meetings are scheduled in the immediate future. Programs will be mailed to all members in the respective territories. Other interested members or non-members may receive copies of programs on request to the Executive Secretary, Mr. Edward R. Loveland, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

Territory	Place of Meeting	Date	Governor	Special Guests
Southeastern (Ala., Fla., Ga., S. C., and Cuba)	Charleston, S. C.	January 26-27	Robert Wilson, Jr.	W. S. Middleton E. R. Loveland
Eastern Pennsylvania	Philadelphia	February 9	Thomas M. McMillan	W. S. Middleton
Maryland and District of Columbia	Washington	February 17	John Minor Wetherbee Fort	E. R. Loveland Geo. Morris Piersol et al.
Nebraska	Omaha	February 17	J. D. McCarthy	L. H. Sloan
Colorado	Denver	February 20	Ward Darley	W. S. McCann
Delaware	Wilmington	February 22	L. C. McGee	M. C. Pincoffs Geo. Morris Piersol E. R. Loveland
Virginia	Roanoke	February 28	C. M. Caravati	—
Kansas	Wichita	March 16	William C. Menninger	W. S. Middleton

PROPOSALS FOR MEMBERSHIP, AMERICAN COLLEGE OF PHYSICIANS

The Committee on Credentials of the American College of Physicians will meet next on March 11 and April 7, 1951. Membership proposals for action at the March 11 meeting must be received at the Executive Office of the College no later than January 10, and for action at the April 7 meeting, no later than February 6, 1951.

GIFTS TO THE COLLEGE LIBRARY OF PUBLICATIONS BY MEMBERS

The following Fellows of the College have recently presented copies of their new books to the College Library of Publications by Members:

Dr. William B. Bean, Iowa City, Iowa, "Sir William Osler: Aphorisms from His Bedside Teachings and Writings."

Dr. Harry J. Johnson, New York, N. Y., "Dietetics for the Clinician."

Dr. Jacob J. Singer, Beverly Hills, Calif., "Differential Diagnosis of Chest Diseases."

Dr. William A. Sodeman, New Orleans, La., "Pathologic Physiology: Mechanisms of Disease."

Dr. Robert H. Williams, Seattle, Wash., "Textbook of Endocrinology."

The College Library of Publications by Members is maintained at College Headquarters. Members frequently present copies of their books to the College and thus the library has become a living memorial to the Member-Authors.

UNIVERSITY OF CALIFORNIA SCHOOL OF MEDICINE ANNOUNCES ITS PROGRAM OF GRADUATE AND POSTGRADUATE INSTRUCTION, 1951

The University of California School of Medicine offers a program of courses of various types and lengths. The courses are made as practical as is consistent with their aim and scope, and are designed to help the physician keep abreast of current, improved methods of diagnosis and treatment of disease. They are not designed to train physicians to become specialists. The only requirements for admission are graduation from an approved medical school and license to practice in one's state. Application blanks may be obtained from Dr. Stacy R. Mettier, F.A.C.P., Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22.

CLINICAL SCIENCE AS APPLIED TO GENERAL MEDICINE: February 5-April 9, Monday evenings.

DIDACTIC RESIDENT COURSE IN OPHTHALMOLOGY: September-January, Monday and Wednesday evenings.

UROLOGY IN PRACTICE: January 23-26.

CARDIOVASCULAR DISEASES: January 29-February 2, mornings. While designed primarily for the cardiologist, it will be of interest also to the general practitioner.

ELECTROCARDIOGRAPHY: January 29-February 2, afternoons.

DISEASES OF THE CHEST: February 19-23; presented through the coöperation of the American College of Chest Physicians.

COURSE FOR GENERAL PRACTITIONERS: March 5-9. An additional course, being planned in coöperation with the American Academy of General Practice, is scheduled for March 26-28.

PEDIATRICS: June 18-22.

GYNECOLOGICAL AND OBSTETRICAL CONFERENCE: August 29-31.

PSYCHIATRY AND NEUROLOGY: August through November, dates to be announced.

OPHTHALMOLOGY: September 10-14; a course for specialists.

EVENING SYMPOSIA IN MEDICINE: September 10-November 26, every Monday evening.

A Training Course for Cardiovascular Investigators, sponsored jointly by the U. S. Public Health Service, American Heart Association, and Western Reserve University School of Medicine, will be repeated for the third time in the Department of Physiology from July 1, 1951 to June 30, 1952. Professor Carl J. Wiggers will be in personal charge. The course will consist of formalized training in research methods used in cardiovascular research, assisting experienced investigators with current research, independent research under supervision, and experience in the preparation of a manuscript.

While primarily organized for postdoctorate training, a few specially qualified predoctorates may be accepted.

Postdoctorate candidates accepted for training will be recommended to the Director of the National Heart Institute, U. S. Public Health Service, for a research traineeship carrying a stipend ranging from \$3,000 to \$3,600 per annum depending on their marital status.

For more detailed announcements or application blanks, address Dr. Carl J. Wiggers, Program Director, Western Reserve University School of Medicine, Cleveland 6, Ohio.

The American College of Allergists offers in Chicago a three day course (February 9, 10, 11) in the basic principles of diagnosis and treatment of allergic individuals. A fee of \$35.00 will be charged. For further information and registration address Dr. Fred Wittich, Secretary-Treasurer, American College of Allergists, LaSalle Medical Bldg., Minneapolis, Minnesota.

The Second International Gerontological Congress will be held in St. Louis, Mo., September 9-14, 1951, provided world affairs permit. This Congress is sponsored by the International Association of Gerontological Societies and by the Gerontological Society, Inc. Physicians wishing to present papers bearing on Gerontology should communicate with Dr. John E. Kirk, Chairman of the Program Committee, Washington University School of Medicine, 5600 Arsenal Street, St. Louis 9, Mo. Those interested in presenting scientific exhibits should get in touch with Dr. Albert I. Lansing, Chairman of the Committee on Exhibits, Washington University School of Medicine, St. Louis 10, Mo.

Dr. George E. Pfahler, F.A.C.P., has been elected Honorary President of the newly formed Graduate School of Medicine-Medico Chi Alumni Society by unanimous vote of the two hundred alumni and faculty present at the Annual Banquet held on September 28, 1950. Dr. Pfahler, at the age of 76, still practices radiology. He graduated from the Medico-Chirurgical College of Philadelphia in 1898. He taught for over forty years at his Alma Mater and the Graduate School of Medicine of the University of Pennsylvania. He was Clinical Professor of Symptomatology (1902-08); Director of the Department of Radiology, Postgraduate Hospital (1899-1903); Director of the Radiological Department, Medico Chi Hospital (1902-1918); Clinical Professor of Radiology, Medico Chi College (1909-1911); Professor of Radiology (1911-16). When the Medico-Chirurgical College and the University of Pennsylvania merged, he became Professor of Radiology and Vice Dean of the Department of Radiology (1916-45). He directed the Radiology Department of the Graduate

Hospital from 1916 to 1932, and that of the Misericordia Hospital from 1916 to 1943. In 1945, Dr. Pfahler became Emeritus Professor and Emeritus Vice Dean, and still attends the Graduate School of Medicine meetings and social functions regularly.

Dr. Pfahler has been President of the American Roentgen Ray Society (1909), of the American Electrotherapeutic Association (1912), of the American Radium Society (1921), and was the first President of the American College of Radiology (1922). He was elected to membership in the Radiological Societies of North America, France, Germany, Russia, Scandinavia, Austria, Mexico and Cuba. He is also an Honorary Member of the Radiological Section of the Royal Academy of Medicine in London and an Honorary Fellow of the Faculty of Radiologists of London. He has an honorary D.M.R.E. (Diploma in Medicine, Radiology, and Electrology) from Cambridge University, England, and an honorary Sc.D. and LL.D. from Ursinus College. The Strittmatter Gold Medal of the Philadelphia County Medical Society was awarded him in 1930, and the Gold Medal of the American Roentgen Ray Society in 1937. The Hall of Science of Ursinus College was named in his honor in 1942. He has been a Fellow of the American College of Physicians since 1923.

Irving N. Holtzman, M.D. (Associate), Brooklyn, N. Y., has been promoted from Assistant Clinical Professor to Associate Clinical Professor of Dermatology and Syphilology at New York University, Bellevue Medical Center. He has also been elected President of the Brooklyn Dermatological Society for 1950-51.

Dr. Russell Wilder, F.A.C.P., Chief of the Division of Metabolism at the Mayo Foundation, spoke November 14, 1950, before the New Haven Medical Society on "The Newer Concepts Concerning Diabetes and the Treatment of This Disease." Dr. Wilder's talk was given in conjunction with the Diabetic Detection Program sponsored by the Connecticut Diabetes Association. Dr. Barnett Greenhouse, F.A.C.P., President of The Connecticut Diabetes Association, presided at a dinner given in honor of Dr. Wilder at The New Haven Lawn Club.

Dr. J. David Markham, (Associate), Richmond, Va., was appointed Instructor in Physiology at the Medical College of Virginia, effective September 1, 1950.

Dr. Edward N. Packard, F.A.C.P., has retired as Medical Director of the Trudeau Sanatorium and has reopened his office at Saranac Lake for the treatment of pulmonary diseases. However, he remains on the Consulting Staff of the Trudeau Sanatorium and as Director of the Trudeau School of Tuberculosis.

S. L. Zimmerman, M.D., F.A.C.P., heretofore Chief of Medicine at the Veterans Administration Hospital, Columbia, S. C., has re-entered active duty in the Army, holds the rank of Lieutenant Colonel and is the Chief of the Medical Service at the Murphy Army Hospital at Waltham, Mass.

Dr. Thomas Durant, F.A.C.P., Philadelphia, has been appointed Director of the Postgraduate Institute of the Philadelphia County Medical Society, succeeding Dr. Gilson C. Engel, F.A.C.S., who has directed the Institute for the last few years.

The Pollak Hospital, the Tuberculosis Unit of Peoria (Ill.) State Hospital, was dedicated on December 3, 1950, in honor of Dr. Maxim Pollak, F.A.C.P., former Superintendent of Peoria Municipal Tuberculosis Sanitarium and a member of the Tuberculosis Advisory Committee of the Illinois Department of Public Welfare.

The American Journal of the Medical Sciences has announced three new appointments to its editorial staff. Dr. Richard A. Kern, F.A.C.P., Professor of Medicine at Temple University School of Medicine, Philadelphia, was appointed Editor, succeeding Dr. Edward B. Krumbhaar, F.A.C.P. The new Associate Editor is Dr. Thomas M. Durant, F.A.C.P. Professor of Clinical Medicine, Temple University School of Medicine, and the Assistant Editor is Dr. Chris J. D. Zarafonitis, Associate Professor of Internal Medicine at Temple University School of Medicine.

The University of Pittsburgh has announced the appointment of three physicians to head its new program in the field of psychiatry and mental health. Named as Medical Director of the University's Western Psychiatric Institute and Clinic is Dr. Henry W. Brosin, F.A.C.P., formerly Professor of Psychiatry at the University of Chicago Medical School. Dr. Brosin will also hold the title of Professor and Head of the Department of Psychiatry in the University of Pittsburgh School of Medicine. Dr. I. Arthur Mirsky, F.A.C.P., formerly Associate Professor of Experimental Medicine in Psychiatry at the University of Cincinnati College of Medicine, was appointed Head of the Research Division of the Psychiatric Institute. Dr. Benjamin Spock, formerly of the Mayo Clinic and the University of Minnesota, was appointed Professor of Child Development.

New York University Post-Graduate Medical School will be host to former matriculates of the three-week course in Allergy, given without interruption for 25 years, under the direction of Dr. W. C. Spain, F.A.C.P. A two-day symposium of recent advances in allergy will be held in Erdmann Auditorium, University Hospital, 303 East 20th Street, on February 2 and 3, 1951, and a 25th Reunion Dinner on Friday evening, February 2.

The Creighton University School of Medicine has announced the appointment of Dr. Harold N. Neu, (Associate), Omaha, Nebr., as the new Head of the Department of Medicine. Dr. Neu has been Director of the Arthritis Clinic and Instructor in Medicine at Creighton University School of Medicine since 1946.

Dr. William H. Perkins, F.A.C.P., Philadelphia, Pa., has resigned his post of Dean of the Jefferson Medical College of Philadelphia because of his health. He will continue on the faculty as Professor and Head of the Department of Preventive Medicine. Dr. Perkins will be succeeded by Dr. George A. Bennett, Professor and Head of the Department of Anatomy.

At the meeting of the Texas Rheumatism Association held in Houston, Tex., on December 8, 1950, Dr. Richard H. Freyberg, F.A.C.P., New York, N. Y., was the honor guest. He spoke on "Practical Considerations in the Use of ACTH and Cortisone in Rheumatic Disease."

Dr. Malcolm T. MacEachern, F.A.C.P., was honored by the Officers, Regents and the Administrative Staff of the American College of Surgeons at a dinner in Chicago on November 19, 1950, on the occasion of his retirement. Dr. MacEachern has been associated with the American College of Surgeons since 1923 when he became Director of Hospital Activities. From 1935-1949 he was Associate Director and Chairman of the Administrative Board, and during 1949 he was appointed Director. In March, 1950, he assumed his present title as Director Emeritus, and was succeeded as Director by Dr. Paul R. Hawley, F.A.C.P.

In recognition of the outstanding public relations project in the use of the graphic arts during 1950, the American Public Relations Association has awarded Smith, Kline & French Laboratories, Philadelphia, the Silver Anvil Award. This is the top award of the Association and was given for the pharmaceutical firm's project of transmitting medical and surgical procedures and clinics to medical meetings throughout the country, using color television.

The Friedenwald Memorial Lecture was delivered at the University of Maryland School of Medicine on November 2, 1950, by Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill., who spoke on "Physiological Basis of the Psychosomatic Aspects of Peptic Ulcer."

Dr. Joseph M. Messick, F.A.C.P., Wilmington, has been elected Treasurer of the Medical Society of Delaware for the year 1951.

The remodeled west wing of the Louisville (Ky.) General Hospital has been named the John Walker Moore Clinic in honor of Dr. Moore, a Fellow of the American College of Physicians and retired Dean of the University of Louisville School of Medicine.

Five Fellows of the College participated in the annual assembly of the Medical Association of Puerto Rico which was held in Santurce, December 12-17, 1950. Among the guest speakers were: Dr. Wilburt C. Davison, Durham, N. C., "Cancer in Childhood"; Dr. Douglas H. Sprunt, Memphis, Tenn., "Evaluation and Application of Tests for the Diagnosis of Cancer"; Dr. Louis H. Clerf, Philadelphia, "The Esophagus and Its Diseases"; Dr. Henry L. Bockus, Philadelphia, "Treatment and Prognosis in Hepatic Cirrhosis"; and Dr. Howard A. Rusk, New York, "Rehabilitation in Chronic Diseases."

Dr. Edward L. Bortz, F.A.C.P., Philadelphia, Pa., was a guest speaker at the monthly meeting of the Jefferson County Medical Society in Louisville, Ky., on November 20, 1950. His subject was "Diabetes Today and Tomorrow."

The American Academy of Allergy will hold its Seventh Annual Meeting in New York, N. Y., February 5-7, 1951. Among the guest lecturers will be Dr. A. McGehee Harvey, F.A.C.P., Baltimore, Md., who will address the meeting on "The Use of ACTH and Cortisone in Allergic Diseases." Other guest lecturers and their subjects are: William F. Hamilton, Ph.D., "The Physiology of the Pulmonary Circulation"; and David Pressman, Ph.D., "The Zone of Localization of Anti-tissue Antibodies as Determined by the Use of Radio-active Tracers."

The Divisions of Postgraduate Study of the Washington University School of Medicine, St. Louis, Mo., has scheduled the following postgraduate courses for 1951:

February 26, 27—ACTH and Cortisone: Principles and Clinical Applications.

March 29, 30—Electrocardiography: Interpretation and Principles of Standard and Unipolar Technics.

Complete programs and further information may be obtained by writing to Dr. B. Eisman, Assistant Dean, Washington University School of Medicine, St. Louis 10, Mo.

OBITUARIES

DR. FREDERIC H. LEWEY

Dr. Frederic Henry Lewey, F.A.C.P., died at his summer home near Pennsburg, Pa., on October 5, 1950. Dr. Lewey was born in Berlin, Germany, January 28, 1885, into a distinguished medical family, his father having been an eminent internist, and Dr. Paul Ehrlich one of its members. After his preliminary education at the University of Berlin, Dr. Lewey received his medical degree from Frederic William University Faculty of Medicine, Berlin; he continued his education by doing extensive postgraduate work in Switzerland, Germany and Holland.

During World War I Dr. Lewey served as a medical officer in the German Army. From 1919 to 1930, Dr. Lewey was Research Assistant, then Associate Professor of Medicine and Director of the Department of Infectious and Nervous Diseases at the University of Berlin. From 1930 to 1933 he was Clinical Professor of Neurology and Director of the Neurological Institute in Berlin. He left Germany in 1933 and, after doing research work in England, he came to the United States in 1934 as Visiting Professor of Neurophysiology at the University of Pennsylvania School of Medicine and Consultant in Neurosurgery at the Hospital of the University of Pennsylvania.

Although it was not in the best interest of his health, Dr. Lewey strongly desired to serve the country of his late adoption, and during World War II he became a Lieutenant Colonel in the Medical Corps, U. S. Army. During this service he was Chief of Neurology at the Cushing General Hospital, Framingham, Mass., and also served as Consultant to the Surgeon General. After the war he was Consultant to the Veterans Administration and the National Naval Medical Center, Bethesda, Md. After his return to civilian life in 1946, he became Professor of Neuroanatomy at the University of Pennsylvania Graduate School of Medicine, and Associate Professor of Neuropathology at the University of Pennsylvania School of Medicine. At the time of his death, in addition to serving his professional duties, he was Director of the Peripheral Nerve Center at the Hospital of the University of Pennsylvania.

Dr. Lewey's position in the field of his principal interest was abundantly recognized. In addition to holding important positions in many American medical societies, including Chairmanship of the Board of Trustees of the American Academy of Neurology, he was a member of the Argentine Society of Normal and Pathological Anatomy and an honorary member of the Argentine Society of Neurology, Psychiatry and Neurosurgery. Dr. Lewey was the author of numerous papers and two of his books, "The Doctrine of Tonus and Movement" and "The Biology of the Person," were very well known. Dr. Lewey was a Diplomat of the American Board of Psychiatry and Neurology and became a Fellow of the American College of Physicians in 1948.

THOMAS M. McMILLAN, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. WILLIAM ALBERT SWALM

Dr. William Albert Swalm, F.A.C.P., died in Philadelphia on August 11, 1950, of coronary thrombosis. Dr. Swalm was born in Philadelphia, April 25, 1888.

After graduating from the University of Pennsylvania School of Medicine in 1911, Dr. Swalm did extensive postgraduate work in this country and in Austria. For many years he was Associate Professor of Medicine, Temple University School of Medicine, and Chief of the Gastroenterological Clinic at the Temple University Hospital. He was a member of the American Gastroenterological Association, the

Society for the Advancement of Gastroenterology, and the International Society of Gastroenterology. Dr. Swalm was a Diplomate of the American Board of Internal Medicine, and became a Fellow of the American College of Physicians in 1935.

THOMAS M. McMILLAN, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. JOHN E. FRETZ

Dr. John E. Fretz, F.A.C.P., died at his home in Easton, Pa., on August 31, 1950, at the age of 76 years, after a long illness. After receiving his preliminary education at the Doylestown Seminary and Lafayette College, he graduated from the University of Pennsylvania School of Medicine in 1897. For many years Dr. Fretz was very active in medical affairs, having held, among other positions, the presidency of the Easton Tuberculosis Society, and the vice-presidency of the Pennsylvania Tuberculosis and Health Society. At one time he had been Physician to Lafayette College. In addition to his medical interests, he also had many outside civic, cultural and religious activities. Although his activities had to be curtailed in recent years, he never lost touch with his medical and extra-medical interests. Dr. Fretz was a Diplomate of the American Board of Internal Medicine, and became a Fellow of the American College of Physicians in 1924.

THOMAS M. McMILLAN, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. MANUEL DE LA PILA-IGLESIAS

Manuel de la Pila-Iglesias, M.D., F.A.C.P., was born in Cadiz, Spain, September 18, 1882, when Puerto Rico was under the Spanish flag. He was brought to this island at the age of 3, where he grew up and received his elementary education. His father was a native of Spain while his mother came from Añasco, Puerto Rico. Dr. Pila became an American citizen in 1917.

Dr. Pila studied medicine in Barcelona, Spain, and in 1906 he obtained the Licenciado in medicine at the University of Barcelona. The doctorate of medicine was received at the Central University of Madrid in 1907. After graduation he went to Paris for post-graduate work where he studied under Professor Dieulafoy at the Hotel Dieu. The influence of French medicine was to remain with him throughout his life. Returning to Barcelona he was appointed instructor in medicine at the University of Barcelona faculty of medicine from 1907 to 1908. During summer vacations he returned to Paris and attended the medical clinics of Dr. Hayem and Professor Roux at the gastro-enterological service of the Hospital St. Antonie. In 1909 he returned to the City of Ponce, Puerto Rico, where he settled down to a general medical practice. In 1919, Dr. Pila visited the Mayo Clinic and while there followed a course in laboratory technic. In 1922 he again went to Europe and under Professor Kumel of Hamburg took up work in internal medicine. At Berlin he studied electrocardiography under Professor Krause, and brought back with him the first electrocardiograph to be used in Puerto Rico. Again in 1925 he spent several months at the Jefferson Medical College in Philadelphia. From 1909 to 1914 Dr. Pila was attending physician to the Tricoche Hospital in Ponce, and he was also a member of the staff of the Home for the Blind and the St. Luke's Hospital in that city. From 1912 to 1926 he was medical director of Hospital Santo Asilo de Damas. In July 1927 he established the Clinica Quirurgica Dr. Pila, being its director until the time of his death. Dr. Pila was Honorary Consultant Surgeon, U. S. Public Health Service.

Dr. Manuel de la Pila Iglesias was a member of the following professional societies: Puerto Rico Medical Association of which he was elected president in 1942 and again in 1943; American Medical Association; Fellow of the American College of Physicians; Fellow of the American Heart Association; honorary member of the American Therapeutic Society; American Hospital Association; president of the Puerto Rico Hospital Council; president of the Puerto Rico Hospital Service (Blue Cross). Dr. Pila was quite active in civic affairs in the City of Ponce, being a prominent Rotarian. He was founder and first president of the Club Deportivo from 1915 to 1931. He also was a prominent member of the Roman Catholic Church, and in coöperation with the church his private clinic was enlarged and a nursing school was founded. He was also a Knight of Columbus, Knight of the Order of San Juan Bautista and a Knight of the Order of St. Gregory of the Roman Catholic Church.

Dr. Pila represented the Puerto Rico Medical Association at the First International Congress of Tuberculosis held in Barcelona in October 1910. He was twice delegate from Puerto Rico to the Annual Meeting of the American Medical Association. Besides being a general practitioner for a number of years and internist with special interest in cardiology, during the later years of his life, Dr. Pila always remained the classical family doctor and he was beloved by his numerous patients and friends. He was active in practice and as director of his private clinic until the end of his life. He met death on October 7, 1950, while returning to Ponce after having attended a meeting of the Puerto Rico Hospital Council at San Juan when his car collided with a parked truck on the highway.

Dr. Pila was recognized not only because he was one of the medical leaders of his generation in Puerto Rico, but also because he possessed other human qualities and virtues such as kindness, sense of humor, understanding and a wide culture, all of which will be remembered by those who knew him.

Dr. Pila is survived by his widow Doña Marina Valdecilla Grau and a daughter.

R. RODRIGUEZ-MOLINA, M.D., F.A.C.P.,
Governor of Puerto Rico

DR. LEWIS ATTERBURY CONNER

Dr. Lewis Atterbury Conner died in The New York Hospital on December 3, 1950, after an illness of several weeks. He was 83 years old.

Born in New Albany, Ind., Dr. Conner received the degree of Bachelor of Philosophy from the Sheffield Scientific School of Yale in 1887. Three years later he was graduated from the College of Physicians and Surgeons of Columbia.

In 1898, the year of its foundation, Dr. Conner began his long association with the Cornell University Medical College here. He was appointed Professor of Clinical Medicine in 1900, occupying that chair until 1916, when he succeeded Dr. W. Gilman Thompson as Professor of Medicine. He held that post until 1932.

Since 1890, Dr. Conner had been connected in various capacities with the New York Hospital. As head of the department of medicine at Cornell Medical College, he was the guest of honor at a dinner given at the Waldorf-Astoria Hotel on April 21, 1932, celebrating the union of the Medical College and the New York Hospital.

He served in the Spanish-American War as a private, and in the first World War as a brigadier general, Army Medical Corps.

Dr. Conner was the founder of the American Heart Journal, which he edited from 1925 to 1938. He was a fellow of the New York Academy of Medicine, a member of the American Medical Association and belonged to the University Club. Dr. Conner had been a fellow in the American College of Physicians since 1928.

Dr. Conner retired from active practice in 1932 and, since that time, limited his work largely to consultations.

A most distinguished physician and friend and a medical educator whose influence in American medicine has been great.

ASA L. LINCOLN, M.D., F.A.C.P.,
Governor for Eastern New York

DR. THOMAS FRANKLIN WALKER

In the death of Dr. Thomas Franklin Walker at Great Falls, Montana, October 22, 1950, the Montana Wyoming region of the College has lost one of its most distinguished and best loved fellows. Dr. Walker died after almost two years of brave battle with a bronchogenic carcinoma of the lung.

Born in Kokomo, Colorado, July 24, 1890, Dr. Walker was the son of Dr. Thomas Franklin Walker, direct descendant of another Dr. Thomas Franklin Walker, who built the first house in Kentucky on order of Daniel Boone. His mother was Elizabeth Lynn Manifold, a direct descendant of Nathaniel Hawthorne.

Dr. Walker had his primary schooling in Kokomo and his High School in Leadville. He entered the University of Colorado Medical School in 1908, graduating in 1912.

After graduating he became assistant professor of Clinical Pathology at his alma mater under Dr. James C. Todd. During 1913 and 1914 he taught in the Department of Pathology at the University of Colorado, and many of the graduates of his school at that time still remember his splendid clear teaching of histology, embryology and pathology. He left his teaching in 1916 to intern at the old Denver County Hospital, now Denver General. On December 7, 1916, he established the Walker Laboratories at Great Falls, Montana, which establishment he guided until his death.

He married Dr. Dora von Holdt in May of 1917, and she has been associated with him in the laboratories throughout the years. The Walkers had five children, one of whom is Dr. Thomas Franklin Walker Jr., who is an associate of the College.

Dr. Walker established the Cascade County full-time Public Health Unit in 1924, and served as county health officer from 1924 to 1928. This unit became, under Dr. Walker, a model for health units in cities the size of Great Falls. During World War II when the then county health officer, Dr. Gibson was called to the Service, Dr. Walker again, in addition to his own tremendous responsibilities, took on the Public Health Unit in Cascade and carried on during 1944 and 1945, those years in which Great Falls was such an important base for flying personnel. He also served on the Selective Service Board during World War II.

Throughout his life in Great Falls Dr. Walker was associated with every worth while project for community betterment. He was the founder of the Great Falls Recreation Association, and was directly responsible for the establishment of several playing fields and the office of Recreation Director. In some way, he found time to serve his city on the School Board and was active in the work of the Great Falls Park Board. The Boy Scout Council also took some of his precious time. He was an active Rotarian and past president of the Great Falls Rotary Club. Other interests included the Great Falls Chamber of Commerce; the Great Falls Executive Club; and the Great Falls Round Table. In early life he developed a taste for reading of good things and with all his community interests he still found time to indulge his appreciation of the things men live by in the world of great literature, music and art.

Always, however, his chief interests were centered around his chosen profession, which he served so well in so very many capacities, and always he brought to medicine his finest sense of scientific honesty and responsibility. He served his County Society

as an active member and as president, his State Society as secretary for four years, and as president from 1949 to 1950. He was a member of the United States Public Health Association and a reserve officer in the United States Public Health Service. He was a founding fellow of the American Society of Clinical Pathologists and was certified by the American Board of Pathology in 1939. He became a Fellow of the American College of Physicians in 1941. From 1920 until near the time of his death he was pathologist to the Columbus Hospital in Great Falls. He was consulting pathologist from 1930 to 1948 to St. Peter's Hospital in Helena, Montana, and to four other Montana hospitals. He was for five years a member of the State Board of Health and for two years its President.

His fraternal affiliations included Omega Upsilon Phi; Acacia Fraternity; Masonic Bodies, both York and Scottish Rites, and the Mystic Shrine.

We hold in grateful memory his kindness, his honesty, his tremendous ability for hard work and his unusual capacity for friendship. I am sure that the passing of no man who has practiced in Montana has left among both lay people and the profession a more poignant sense of personal loss.

H. W. GREGG, M.D., F.A.C.P.,
Governor, Montana and Wyoming

DR. THEOPHIL J. HOLKE

On September 9, 1950, Dr. Theophil J. Holke died of coronary heart disease in the Deaconess Hospital at Freeport, Illinois. A Fellow of the American College of Physicians, Dr. Holke was most faithful in attending the Annual as well as Regional Meetings of the College. He was born in Waterloo, Illinois, April 16, 1876, received his degree in medicine at Washington University School of Medicine (1899), and studied in Austria for one year (1913-14). He settled in Freeport and was a member of the Board of Trustees of the Deaconess Hospital for twenty years, and Chief of Staff of this hospital from 1932 to 1944. Dr. Holke served as examining physician for the Illinois Central Railroad for over twenty-five years. He was a member of St. John's Evangelical and Reformed Church and an active member in Masonic circles in Freeport. He is survived by his widow, Flora Hermsmeier Holke, whom he married in 1902, and by two sisters.

CLARENCE H. BOSWELL, M.D., F.A.C.P.,
Rockford, Illinois

DR. FARIS F. CHESLEY

Dr. Faris Franklin Chesley, F.A.C.P., Chicago, Ill., was born November 3, 1897, in Armour, South Dakota. He graduated from the University of Nebraska in 1919 and from Rush Medical College in 1921. Dr. Chesley spent the years of 1925 and 1926 in Vienna where he obtained postgraduate training in the specialty of internal medicine, particularly in diseases of the chest. For many years, he was an active member of the faculty of Northwestern University Medical School. He was a member of the staff of the St. Luke's and Cook County Hospitals, Chicago.

Dr. Chesley was a Fellow of the American Medical Association, a member of the Chicago Medical Society and Illinois State Medical Society, and, since 1941, a Fellow of the American College of Physicians.

In the last two years of his life, Dr. Chesley passed through a heart breaking sequence of diseases and complications culminating in his death in St. Luke's Hospital on September 12, 1950. The ordeal began with pulmonary tuberculosis contracted, apparently, at Cook County Hospital, which he served most loyally and

devotedly for thirteen years. An associate and a resident developed the same disease simultaneously. While still convalescing from the pulmonary disease, Dr. Chesley developed an obscure gastric neoplasm and, terminally, cerebral embolism. His courage and fortitude through this long period were an inspiration to his friends and family.

He is survived by his widow, Ellouise Ballstadt Chesley, whom he married in 1931, by his twin children, Faris and Jane, 12 years of age, and by four sisters and one brother.

Dr. Chesley was a cheerful, delightful companion, a good friend, a splendid physician, and a devoted father of his family. He is remembered with affection by all who were privileged to know him.

WALTER L. PALMER, M.D., F.A.C.P.,
Governor for Northern Illinois

DR. EDWARD SANBORN SMITH

Dr. E. Sanborn Smith, F.A.C.P., Kirksville, Mo., died July 23, 1950. He was born in Salina, Kans., April 25, 1875, and received his medical degree from the University of Maryland School of Medicine in 1900. For many years he was a member of the Staff of the Grim-Smith Hospital and Clinic at Kirksville.

Dr. Smith for many years was a member of the Missouri State Board of Health and served as President of the Board in 1937. In 1941, he was Vice President of the Mississippi Valley Medical Society. He was a member of the American Association for the Advancement of Sciences and of the Association of Military Surgeons of the United States. He was a Fellow of the American Medical Association and had been a Fellow of the American College of Physicians since 1934 and a Life Member since 1940. Dr. Smith's death was due to cerebral hemorrhage.

DR. DOUGLAS MEHARG GORDON

Dr. Douglas Meharg Gordon, F.A.C.P., died of coronary thrombosis at his home in Ponca City, Okla., October 28, 1950.

Dr. Gordon was born in Toronto, Ontario, August 15, 1901. He attended the St. Andrews College in Toronto and graduated from the University of Toronto School of Medicine in 1927. He took his internship at the Church Home and Infirmary at Baltimore, Md., and served his residency at the University Hospital in Oklahoma City during 1929.

Immediately after completing his residency, Dr. Gordon became affiliated in July, 1929, with the Niemann-Northcutt Clinic, where he served as a specialist in internal medicine for the past twenty-one years.

During World War II, Dr. Gordon served as a Lieutenant Colonel in the Medical Corps, U. S. Army. He entered the service in May, 1942, and spent 26 months in the China-Burma-India theater. He returned to his office in November, 1945.

Dr. Gordon was a member of the Presbyterian Church, the Rotary Club, the Kay-Noble County Medical Society, the Oklahoma State Medical Association and the American Medical Association. He was a member of the board of directors of the Oklahoma Heart Association, and had been a Fellow of the American College of Physicians since 1935.

WANN LANGSTON, M.D., F.A.C.P.,
Governor for Oklahoma

CONDENSED MINUTES, BOARD OF REGENTS, PHILADELPHIA, PA., NOVEMBER 12, 1950

The regular autumn meeting of the Board of Regents of the American College of Physicians was held at the College Headquarters in Philadelphia, Pa., Sunday, November 12, 1950, with President William S. Middleton presiding, and Mr. E. R. Loveland acting as Secretary. Those in attendance included William S. Middleton, President; Maurice C. Pincoffs, President-Elect; Ernest H. Falconer, First Vice President; Arthur T. Henderson, Third Vice President; William D. Stroud, Treasurer; George Morris Piersol, Secretary-General; Marion A. Blankenhorn, Walter B. Martin, Hugh J. Morgan, LeRoy H. Sloan, Wallace M. Yater, Edward L. Bortz, William S. McCann, T. Grier Miller, Charles F. Moffatt, A. B. Brower, Alex. M. Burgess, Reginald Fitz, George H. Lathrope, Cyrus C. Sturgis, Charles A. Doan, Vice Chairman of the Board of Governors; Thomas M. McMillan, Chairman, Advisory Committee on Postgraduate Courses; Richard A. Kern, Chairman of the Committee on Military Affairs, and Ralph A. Kinsella, General Chairman of the 32nd (1951) Annual Session.

Abstracted minutes of the previous meetings of the Board were read and approved.

Numerous communications were read and appropriate action taken where indicated.

The Board voted an appropriation of \$1,000.00 toward the support of the World Medical Association for the year 1951, without specific recommendation for succeeding years.

Dr. George Morris Piersol, Secretary-General, was appointed as official representative of the American College of Physicians to serve on the Committee on Purchasing Simplification and Standardization of the Council on Administrative Practice of the American Hospital Association.

The Board of Regents approved the appointment by the President of a Committee on Military Affairs, consisting of Richard A. Kern, Chairman, Philadelphia, Pa., F. Dennette Adams, Boston, Mass., William S. McCann, Rochester, N. Y., Elbert L. Persons, Durham, N. C., and Benjamin H. Rutledge, Baltimore, Md.

Reports were received from official representatives of the College as follows: From Dr. Edward A. Greco, F.A.C.P., Portland, Maine, on the First International Congress on Diseases of the Chest, Rome, September 17-22, 1950; from Dr. William C. Menninger, F.A.C.P., Topeka, Kansas, on the Mid-Century White House Conference on Children and Youth, December 3, 1950; from Dr. Fuller B. Bailey, F.A.C.P., Salt Lake City, Utah, on the Diamond Jubilee of Brigham Young University and on the installation of the new President of the Utah State Agricultural College; from Dr. Alex. M. Burgess, Sr., F.A.C.P., Providence, R. I., on the World Medical Association's Meeting in New York City, October 16-20, 1950; from Dr. Chester S. Keefer, F.A.C.P., Boston, Mass., and the late Dr. Walter W. Palmer, F.A.C.P., New York City, on the United States Pharmacopoeial Convention, Washington, May 9-10, 1950; from Dr. Fred E. Ball, F.A.C.P., Chicago, Ill., on the Sixth Semi-Annual Meeting of the Council on National Emergency Medical Service, Chicago, May 6, 1950.

Dr. George Morris Piersol, Secretary-General, reported the deaths of 53 Fellows and 11 Associates since the last meeting of the Board. Their names were recorded in the minutes and a resolution was adopted providing for the appointment of a committee to prepare memorials on Dr. Allen A. Jones, former A.C.P. Governor for Western New York; Dr. Francisco de P. Miranda, former A.C.P. Governor for Mexico; and Dr. Walter W. Palmer, former Regent and former President of the

College. The Secretary-General's report also included the names of 12 additional Life Members since the last meeting of the Board, making a grand total of 875, of whom 82 are deceased, leaving a balance of 793.

The Executive Secretary presented a report covering: (1) the appointment of Mr. H. Kurtz Canby, on May 22, 1950, as an Executive Assistant, in accordance with authorization from the Board of Regents; (2) regional meetings for the year 1950 and those scheduled in the early part of 1951; (3) the publication, during 1950, of a supplement to the 1949 Directory of the College; (4) the possibilities and problems of publishing a new and revised Directory of the College in 1951; (5) the gift to the College Headquarters of a portrait of the Secretary-General, Dr. George Morris Piersol, by the Piersol Testimonial Committee of Philadelphia.

The following report was made by President Middleton, as Chairman of the Executive Committee of the Board of Regents, relative to the Advisory Board for Medical Specialties:

"Members of the Executive Committee have had a wide discussion of this matter, which was first raised by Dr. Hugh J. Morgan, and rightfully so, because the Advisory Board for Medical Specialties had apparently failed of its mission.

"I should like to ask your indulgence for a few moments to trace its history. The Advisory Board is the creature of the original Certifying Boards that set up specialty certification. In the Minutes of the House of Delegates of the American Medical Association for the Milwaukee meeting in 1933, there was notice taken of this particular direction of movement in a resolution to support and to endeavor to correlate the work among these specialty boards. In 1933 the first meetings of the interested groups were called, and the Constitution and By-Laws were adopted on February 11, 1934, at which time there were representatives from the Association of American Medical Colleges, the American Hospital Association, the Federation of State Boards of Medical Examiners and the National Board of Medical Examiners and four of the specialty boards, namely, the American Board of Ophthalmology, established in 1917, the American Board of Otolaryngology, established in 1924, the American Board of Obstetrics and Gynecology, established in 1930, and the American Board of Dermatology and Syphilology, established in 1932. After 1934, there apparently was a regular rash of specialty boards, and accordingly the design of the Council on Medical Education and Hospitals of the American Medical Association to keep these within rather certain limits of coordination.

"The purposes of the Advisory Board for Medical Specialties were three: (1) to avoid confusion and duplication; (2) to coordinate, and (3) to advise groups and boards that were in the process of formation. There were no policing powers given to the Board, and from the beginning it has been the Advisory Board in fact, as well as in name.

"There were two members of each Board named, usually the President and the Secretary. These men then were regularly taken in and constituted the functioning group with the Presidency in the hands of Dr. Robin C. Buerki, and the Secretary-Treasurership in the hands of Dr. Byrl R. Kirklin. The Secretariat has only a part-time Secretary, and the budget is about \$2,000.00 a year. As they have functioned in the past, they have advised presumptive Boards as to the manner in which they could properly organize and then, having cleared them, have taken up their qualifications and their objectives with the Council on Medical Education and Hospitals of the American Medical Association, with which in recent years they have worked very closely.

"It is rather significant that the Council has never had membership, and the reason for this is a clear one administratively, because the Council never wished to be placed in the position where it would be a minority and outvoted if they were

opposed to the granting of this privilege to any new group. It has acted then as a sort of brake upon the Advisory Board, because notification of acceptance must be cleared through both of them, and they have worked very closely together.

"The financial support was first through the Macy Foundation, and, obviously, the hand of Dr. Rappleye is clear there, and then after a certain amount was levied upon the Diplomates, those receiving the certificate from each of the several Boards until 1948, since when their subsidy has come from the royalties on the sale of the Directory of Medical Specialists.

"This, then, is a brief outline of exactly how the Advisory Board for Medical Specialties came into existence. There is no question of its need. Its functions were rather clearly defined in our report, but the real weakness has obviously been picked up by Dr. Morgan in his statement that they have no policing power. They have no design for policing power. They have, however, according to the advices of Dr. Kirklin, carefully gone into the area of increasing their range of activities, and the support of several Specialty Boards is being sought in this direction. I believe they realize as much or more than any one outside the Advisory Board just how weak they have been in the past, but I have assurance from Dr. Kirklin that this movement has already been initiated, largely through Dr. Morgan's objections, I might say, within the Board, and they simply express regret that he was not available to them to carry through his crusade, which had really been initiated at his instance. This then, gentlemen, is the situation as it has been, as it is currently and as the future is projected. I do not believe they can be coerced into any more rapid meeting of their obligations, and I doubt whether any of the individual Boards would tolerate domination from a majority, but I do believe that with constructive thinking at the top we may expect action.

"In the first place, I believe that they are going to seek increasing support, so that they may have a full-time Secretary, and in the second place, there is distinct design on the part of Dr. Kirklin, at least expressed in personal letters, that the movement has been initiated to give them increasing power. They do not desire to usurp authority over the individual Boards, but they should have better control."

Dr. George Morris Piersol, Chairman of the Committee on Credentials, presented the report of that Committee at this time. First, he read a condensed set of qualifications for Associates, as a guide for Governors, sponsors and candidates. It was reviewed section by section and approved, and the Executive Secretary was instructed to proceed with the printing thereof, to distribute it to all members of the Board of Governors, and to utilize it in instructing sponsors and candidates.

The Committee had reviewed three applications by Associates for extension of their terms, due to extenuating circumstances of illness. The Committee recommended to the Board of Regents such extension, details of which are recorded in the minutes, including the resolution granting official approval by the Regents.

The Committee on Credentials reviewed 316 proposals for Associateship, recommended the election of 244, the deferment of 58, and the rejection of 14. The list of those recommended for election was scrutinized by the Regents and their election was consummated (the list has been published in a preceding issue of this journal).

The Committee on Credentials had also reviewed 206 proposals for Fellowship, and recommended to the Regents the election of 143 (8 for Direct Fellowship and 135 for advancement from Associateship), the deferment of 50 and the rejection or withdrawal of 13. The list of those recommended for election was scrutinized by the Regents and by resolution the entire list was elected to Fellowship.

Of the Associates who had been elected five years prior to this meeting, namely on November 18, 1945, the Committee reported that 70 had qualified for advancement to Fellowship, the terms of 9 had been extended due to military service, 2 were deceased, 10 had been dropped for failure to qualify, and 8 had resigned; total, 99.

Dr. Piersol then presented the names of 35 Associates who, having failed to qualify for advancement to Fellowship in the maximal period allowed under the By-Laws, were dropped at this meeting. Dr. Piersol pointed out that it may be possible for these Associates later on to return to College membership. If an Associate is dropped, he can be re-proposed for Associateship at a later time, when he has fulfilled the requirements, and may then progress to Fellowship in the regular manner.

Dr. Cyrus C. Sturgis, Chairman of the Committee on the Alfred Stengel Memorial Award, reported for that Committee and presented the nominations of four candidates. These were voted upon by secret ballot and the recipient selected. His name will be announced at the next Convocation of the College, when the award will be made. Regulations governing the Alfred Stengel Memorial Award provide that no announcement may be made as to the name of the recipient until the time of the official award.

Dr. Charles F. Moffatt, Chairman, reported for the Committee on Masterships. Growing out of the report and recommendations of that Committee, Dr. Ernest E. Irons, Chicago, former Regent and former President of the College, was chosen for a Mastership to be awarded at the 1951 Convocation.

The Committee also presented the recommendation that Sir John Parkinson, of London, England, who will be a guest at our 1951 Annual Session, shall be elected to Honorary Fellowship. This recommendation was unanimously approved by resolution. Sir John Parkinson is a highly respected international cardiologist. He is an F.R.C.P. of London, M.R.C.S. of England, and Consulting Physician to the Cardiac Department of London Hospital. He holds a great many honors and is internationally known.

Dr. Cyrus C. Sturgis, Chairman, reported for the Committee on Fellowships and Awards, dividing his report into two main sections: (1) the Latin-American Fellowship Program and (2) the A.C.P. Research Fellowship Program. Doctor Sturgis reviewed the work that has been done in connection with the first group of Latin-American Fellows working in this country. In specific cases, three fellowships had been extended for further study. Their record of accomplishment has been particularly gratifying. At a meeting of the Committee at Ann Arbor, Mich., on July 29, 1950, 8 new Latin-American Fellows had been approved. Doctor Sturgis further reported on the programs that have been arranged for those Latin-American Fellows who are shortly to complete their orientation course. Summarizing the Latin-American Fellowship Program, he pointed out that we have sixteen in various stages of their training, five have been placed under preceptors and will finish their work within the next few months, most of them having been in this country for eighteen months, their expenses being paid by the Kellogg Foundation. They receive \$155.00 a month but there is an additional appropriation of \$60.00 if they are accompanied by their wives; they receive compensation for approved travel; their textbooks are bought; each man, at least once, may attend the Annual Session of the American College of Physicians, and may register for some of the Postgraduate Courses offered by the College. Five of the Fellows have been placed and will soon finish; six are attending the Orientation Course at Cornell University; five were assigned directly without orientation because they did not particularly require that course; three attended the Language School of the University of Michigan; there have been four Fellows from Brazil; four from Mexico; three from Chile; one from Venezuela; one from Peru; one from Colombia; one from Paraguay; and one from Canada. Four have been interested in General Medicine; four in Gastro-intestinal Diseases; three in Pathology; two in Physiology; one in Hematology; one in Cardiology; and one in Peripheral Vascular Diseases. Their final assignments have been as follows: three at the University of Michigan; three at the University of Pennsylvania; three at Harvard Medical School; one at Cornell University; one at Mount Sinai Hos-

pital, New York City; one at Presbyterian Hospital, New York City; one at the Mayo Clinic; one at Washington University, St. Louis; and one at the University of Illinois; one remains yet unassigned.

Dr. Sturgis reported a gift of some sixty dollars from Dr. Charles H. Drenckhahn, to be added to the Research Fellowship Fund. He then reported on each of the Research Fellows, who concluded their fellowships during 1950, and on the new group of six research Fellows who started July 1, 1950. He expressed gratification that all of the men that the Committee had selected have shown great promise. Most of them have published papers, or at least have started on a problem that seems to be of promise. He felt the Committee had picked candidates of whom the College may be proud, candidates who will accomplish a great deal for medicine in the future.

Dr. Sturgis reported that the Executive Secretary, Mr. E. R. Loveland, and a member of the Committee on Fellowships, Dr. T. Grier Miller, had made a comprehensive survey of medical fellowships over this country, with special reference to annual stipends. As a result, it was the opinion of the Committee that the stipends offered by the College had been somewhat lower than comparable stipends from other sources; the Committee recommended to the Regents that the College's stipends for Research Fellowships, beginning July 1, 1951, should be \$3,000.00 for unmarried candidates and \$3,500.00 for married candidates; and, furthermore, that the Alfred Stengel Research Fellowship shall carry an additional \$500.00. By resolution, this recommendation was approved by the Regents.

The Committee had considered 46 applications for the A. Blaine Brower Traveling Scholarship and had unanimously selected Dr. Benjamin B. Wells, Little Rock, Arkansas, for recommendation to the Regents as the first recipient of this scholarship. This scholarship will afford an opportunity for Dr. Wells, who is a full-time Professor of Medicine at the University of Arkansas, to visit other medical schools to investigate methods of teaching, etc. There were many other meritorious requests, and Dr. Sturgis said the Committee could have readily selected many other deserving candidates.

By resolution, the Regents approved of the award of the A. Blaine Brower Traveling Scholarship to Dr. Wells.

Dr. Sturgis referred again to the large number (46) of applications for the above scholarship, which indicated its need and popularity. The Committee, therefore, being impressed by the possibilities and the merit of the candidates, recommended to the Regents: (1) an additional sum of \$10,000.00 be set aside to establish a second traveling scholarship; (2) that the Brower Traveling Scholarship stipend for 1951 shall be \$400.00; (3) that the Finance Committee reinvest the Brower Fund in high yielding securities and not restrict it to government bonds, yielding only 2½ per cent; (4) that the second \$10,000.00 recommended under (1) above also be invested in high yielding securities; (5) that each of the traveling scholarships be known as the A. Blaine Brower Traveling Scholarships (this was approved in principle and later included in the report of the Committee on Finance, and the recommendations were all authorized).

From a list of 25 applicants for Research Fellowships, the Committee had selected the following and recommended approval by the Board of Regents:

1. *John William Athens*; 26; a graduate of Johns Hopkins University School of Medicine, 1948; to work under Dr. F. W. Barnes, Jr., Johns Hopkins Hospital, to study the phenomenon of protein regeneration, an understanding of which requires accurate measurement of the replacement rates of various components of a protein molecule.
2. *Amos Immanuel Chernoff*; 27; a graduate of Yale University School of Medicine, 1947; to work under Dr. Carl V. Moore, Washington University School of Medicine, in the group of hemolytic anemias.

3. *John William Harris*; 30; a graduate of Harvard Medical School, 1944; to work under Dr. William B. Castle at the Thorndike Memorial Laboratory in the field of Hematology.
4. *Sidney Harold Ingbar*; 25; a graduate of Harvard Medical School, 1947; to work under Dr. Maxwell Finland, at the Thorndike Memorial Laboratory, Boston City Hospital, on a further investigation into the metabolic physiology of infection and into the rôle of the endocrine glands in the response of the organism to infection.
5. *John Edmund Kiley*; 30; a graduate of Harvard Medical School, 1945; to work under Dr. A. V. Wolf and Dr. William B. Deichmann, Albany Medical College, on a research concerned with the understanding and management of medical aspects of renal disease.
6. *James Edwin Wood, III*; 25; a graduate of Harvard Medical School, 1946; to work under Dr. Robert W. Wilkins, Evans Memorial, Massachusetts Memorial Hospitals, Boston, on plethysmographic studies of the circulation in the extremities.

The following candidate, *Dr. John William Harris*, was selected from the above group of six to be designated as the Alfred Stengel Research Fellow, on account of his outstanding qualifications.

The Committee recommended a total appropriation of \$20,500.00 to be expended for these fellowships.

By resolution, unanimously carried, the recommendations of the Committee on Fellowships and Awards regarding Research Fellowships, starting July 1, 1951, were approved.

By formal resolution, unanimously carried, the selection of Dr. Lawrence was approved.

Dr. Sturgis, continuing his report, stated that the Committee had studied a long list of nominees for the James D. Bruce Memorial Award for outstanding work in the field of Preventive Medicine, and had unanimously agreed to nominate to the Board of Regents, Dr. Rolla E. Dyer, formerly of the U. S. Public Health Service and now associated with Emory University School of Medicine, Atlanta, to be the fourth recipient of this award.

By resolution, unanimously carried, Dr. Dyer was selected as the Bruce Medalist for 1951.

Dr. Marion A. Blankenhorn, as Chairman of the Committee on Educational Policy, made the following report:

"The Committee on Educational Policy has, as is customary, advised with the Advisory Committee on Postgraduate Courses to devise specific courses. The Committee has recently reviewed its duties as put upon it in 1940 by the Regents, and now restates some of its accepted principles. First, we believe that the College by its present methods, that is, through its journal and its Annual Sessions, is accomplishing its educational functions, and the Committee offers advice only when requested. Second, we do recommend to the leaders of Regional Meetings that such meetings are not meant to duplicate or to substitute for the Annual Session, and that, insofar as possible, Associates and young men be given opportunity on the programs. Third, we recommend to the Regents, on considering the changing world, that the educational plans of the College give more effort to educate its members in current medical political issues, to the end that its members may take leadership in such matters, each in his own community."

This report, by resolution, was adopted.

Dr. Thomas M. McMillan, Chairman, reported for the Advisory Committee on Postgraduate Courses. He reviewed the sixteen courses given on the 1950 schedule, with a registration of more than one thousand physicians. In discussing the projected program for the future, he expressed as an objective of the Committee a good geographical distribution of courses in various parts of the country, and a diversification of the institutions where courses are given and the directors of such courses. He presented a group of nine proposed courses for the spring of 1951, and discussed the courses, the contents, the facilities and the directors. He also submitted an outline of proposed courses for the Autumn of 1951, and of other courses planned for the immediate future. His report, by resolution, was approved. (The list of Postgraduate Courses for the spring of 1951 has been published elsewhere in this journal.)

Dr. LeRoy H. Sloan, Chairman, reported for the Conference Committee on Graduate Training in Medicine, this Committee working with the Council on Medical Education and Hospitals of the American Medical Association, especially in relation to passing on hospital residencies. He reviewed the problems of the Committee and reported progress toward the improvement and extension of the work. He bespoke the active coöperation of the Governors and of the Regents of the College in connection with inspection of hospitals in certain areas.

Dr. Sloan, who is also Chairman of the Committee on Public Relations, then reported for that Committee. On recommendation of the Committee the Regents accepted the proposal of Dr. George E. Farrar, Jr., F.A.C.P., Medical Director, Wyeth, Incorporated, to make a sound highlight film of our St. Louis Annual Session, 1951, provided that the editorial control rests with the College, including the selection of speakers and the final inspection of the finished film prior to release. It was recorded that the film will be exhibited before medical societies, medical schools, hospital staff meetings, etc., and a copy given to the American College of Physicians. There will be nothing on the film of an advertising character, except a mere credit line to the effect that the film was prepared under a grant by Wyeth, Incorporated.

On recommendation of the Committee on Public Relations, dues of five members were waived, because of physical incapacitation.

On recommendation of the Committee, the resignations of twenty-five Associates, who had failed to attain certification and thus were unable to qualify for advancement to Fellowship, were accepted. The resignation of one Associate, who was not in good standing, could not be accepted as a resignation, and the Associate had to be dropped at the end of his term. The resignation of one Associate was held in abeyance, granting extension of time, pending clarification of status with regard to American Board examinations.

President Middleton reported as follows on the status of the hospital inspection program heretofore administered by the American College of Surgeons:

"A matter of great importance to the College, by reason of policy, came to our attention by direction, or indirection, during the summer months and early autumn. The Executive Secretary received word of an attempt to consolidate the survey, inspection and certification of hospitals as acceptable in terms of given functions, this program heretofore directed by the American College of Surgeons. This movement apparently gained momentum out of proportion to the acceptance on the part of parent groups, and then in a public press notice Dr. Sloan observed that the American College of Physicians was included among those groups that were to inspect and to certify to the adequacy of hospital services, whereupon he called me on September 29 and, as Chairman of the Committee on Public Relations, was authorized to sit in as an observer upon a meeting called in Chicago. The movement gained further momentum, and a Washington, D. C., meeting was held, to which Dr. Sloan could not re-

spond, and I asked four of our Fellows, Dr. Reginald Fitz, Dr. George Morris Piersol, Dr. Maurice C. Pincoffs and Dr. Wallace M. Yater, to attend this meeting as representatives of the College. Dr. Yater acted as Chairman of the group and rendered a very complete report. Dr. Pincoffs gave a very clear analysis of the situation, which can be summarized very briefly by indicating that the American Hospital Association, having ostensibly acquired the direction of the hospital program from the American College of Surgeons, had proposed a commission composed of twelve members of the American Hospital Association, six hospital trustees, three representatives from the American College of Surgeons and three from the American College of Physicians. This meant that there would be six physicians sitting across the table from twenty-five representatives of hospitals. Of course, there could be no sale on this program. Representatives of the American Medical Association apparently proposed a compromise, which was to represent more equal distribution of membership on the commission, but, obviously, none of these agencies was in a position to deal, and the American Hospital Association maintained its adamant position that it would do inspections on its own in a physical sense, with no assurance that they were not going to enter into the professional and educational program of hospitals. The net result of this Washington meeting was a consolidation of the position of the representatives of the American Medical Association and the advice from our representatives through the Chairmanship of Dr. Yater that the American College of Physicians continue exploration and contact of this movement, helping by advice, guiding, if they could, the direction of movement.

"Therefore, upon representation of General Hawley of the American College of Surgeons, I requested Dr. Sloan to keep this contact, and at a meeting on November 1, he was advised that there would not be any matters of importance brought up, but there would be final hearing in the total picture on November 19, at which time it is my request that the Committee on Public Relations of this College be well represented to bring this matter into sharper focus for a number of you. I hope, if there are additions to be made from representatives of the College, Washington or Chicago, they will enlarge upon it, in the hope that there will be given authority for this representation, which, obviously, is not entirely medical. It is in the area of public relations with the laity, so you can see how the American Hospital Association wished to seize and usurp for themselves the total hospital program of inspection. I believe that the delegation of this authority to Dr. Sloan, as Chairman of the Committee on Public Relations, and his Committee as a whole, is in order."

... A motion was offered by Dr. Wallace M. Yater, duly seconded and opened for discussion, approving the suggestion of President Middleton. ...

Dr. Walter B. Martin, Chairman of the Committee on the Annals of Internal Medicine, reported that the progress of the ANNALS during the past year had been most satisfactory from the standpoint of content, subscriptions and financial status. In accordance with the plan outlined by the Committee last year, the number of scientific articles had been increased to fourteen and the case reports to six. This had resulted in a reduction of the waiting time for publication to an average for the scientific papers of less than ten months and of case reports to about seventeen months. With a continuation of the policy, the Committee felt that within a reasonable time the accumulated excess of accepted material can be absorbed. The Committee recommended that the present level of publication of contributions be continued, and that the Editor be authorized to reduce this number gradually when a satisfactory level of acceptable material is reached.

Dr. Martin said a satisfactory increase (20 per cent) in the amount of advertising had been received, this occurring in the face of a falling off in the advertising

volume of most other medical publications. He reported the financial position of the *ANNALS* as gratifying, the journal now showing a substantial profit. On the recommendation of the Committee, a new layout of the back page of the journal, as submitted by the Editor, was approved. The report of the Committee was approved by resolution.

President Middleton, as Chairman of the Consulting Committee on Annual Sessions, presented the Board with a tentative program of morning lectures and general sessions for the forthcoming 1951 Annual Session, and pointed out special features and explained his objectives in the formation of the program. He expressed the hope that the Regents may some time decide to delegate to the Committee on Educational Policy the status of a standing committee, so that there may be advice for the Annual Sessions and correlation of programs over succeeding years, believing this plan to have superior merit over the present Consulting Committee, which offers representation only of the two preceding years.

Dr. Ralph A. Kinsella, General Chairman of the 1951 Annual Session, presented an outline program of clinics, panel discussions and colored television, and announced the Chairmen personnel of the various Committees.

President Middleton reported that 205 members of the College, who attended the Annual Session in Boston, 1950, were consulted about various features of the program. Responses had been enlightening and helpful. Only two members had supported his suggestion that there should be a curtailment or abolition of technical exhibits. He expressed the belief that the College can do a real service for the exhibitors if it indicates to them that the level of our intelligence is not merely visual perception. The questionnaire had been very helpful in obtaining opinions and determining preferences concerning the various features of the program. It was revealed that few of the members apparently had any inherent interest in the Convocation and the Reception, and some other features of that type. The overwhelming majority favor the present pattern of the general sessions. There was an interesting division of interest in television. Many felt that the colored television program could be developed a great deal from a technical standpoint. There appeared to be a lessening interest in the program of clinics. Many felt the clinics lose effectiveness because they are often converted into lectures, and these men who are intelligent internists are not going to clinics any longer simply to have a man stand up and give an abstract lecture.

Dr. Middleton recommended that this sort of analysis should be duplicated periodically by the Executive Office, perhaps not every year; the information is not only useful, but it encourages members of the College to express critical attitudes toward our educational offerings. Dr. Middleton also referred to the matter of scientific exhibits. They were tried by the College in Montreal in 1933, were not very abundant, nor very detailed. He said there has been some pressure from time to time to introduce scientific exhibits in the College program. This would be a very exacting performance and if the College entered into it, the College would have to go wholeheartedly and set up an organization that had continuity and purpose.

The matter of scientific exhibits was discussed among several members of the Board, and the consensus was unfavorable to the College initiating such a program.

The following report was received from the Treasurer, Dr. William D. Stroud:

"This report is supplemental to that of the Committee on Finance. The cash balance on November 1, 1950, was as follows:

Endowment Fund	\$ 1,475.05
General Fund	124,469.23
	<hr/>
	<u>\$125,944.28</u>

"It is estimated that the receipts from now to the end of December, 1950, will total approximately \$31,000.00 and the expenditures approximately \$74,000.00. The Committee on Finance will make recommendations concerning the investment of surplus funds not required for operation, and it will also report on the security transactions since the last meeting of this Board.

"The present security holdings of the College are as follows:

	<i>Book Value</i>	<i>Market Value</i>	<i>Appreciation</i>
Brower Fund	\$ 10,000.00	\$ 10,000.00	
Bruce Fund	10,000.00	10,000.00	
Endowment Fund	328,248.67	348,300.25	\$20,051.58
General Fund	240,882.35	269,718.00	28,835.65
	<u>\$589,131.02</u>	<u>\$638,018.25</u>	<u>\$48,887.23</u>

"The annual cash income from securities, on our present holding basis, is estimated by our Investment Counselor as \$28,600.00, with an average yield of 4.58 per cent. Representatives of Drexel & Co., our Investment Counselor, make regular analysis of our accounts, and met with the Finance Committee at its meeting yesterday."

Dr. A. B. Brower, Chairman of the Committee on Finance, reported for that Committee. The Committee offered for clarification of the guest fee regulations at the Annual Sessions the following:

There shall be *no registration fee exacted*:

- From Medical Officers of the Army, Navy, U. S. Public Health Service, Air Force or Veterans Administration;
- From members of the staffs of participating hospitals in the city of the meeting; courtesy staff members will not be admitted free;
- From graduate medical students of the local institutions of the city where the meeting is held, or from residents in the local hospitals.

In view of the fact that non-member attendance is limited, the above does not include the admission of graduate medical students or residents from institutions in other cities than that where the College is meeting. It was further pointed out in discussion that the above refers directly to "the city of the meeting," and does not include suburban and other near-by areas. This interpretation of the regulations was approved by the Regents by formal resolution.

Dr. Brower reported on the recommendations of the College Investment Counselor with regard to investment of \$26,000.00, which recommendations had been approved by the Committee and were likewise approved by the Board of Regents. The Committee had discussed with the Investment Counselor also the proposal that instead of treating the Bruce Memorial Fund and the Brower Scholarship Fund as individual trust accounts, invested in specific securities, these funds should be made a part of the general Endowment Fund, to participate pro rata in the income from the Endowment Fund securities. This would increase the rate and amount of income of these two funds, over the present plan of having them specifically invested in U. S. Government Bonds. This recommendation was approved by the Committee and by the Board of Regents.

Dr. Brower then presented an outline of all security transactions that had taken place since the last meeting of the Board of Regents. Submitted for record and approval of the Board were especially the Endowment Fund transactions. These were formally approved by the Regents.

The Finance Committee had received a recommendation that an additional fund of \$10,000.00 be segregated from the Endowment Fund to provide for an additional traveling scholarship, to be combined with the traveling scholarship founded by Dr. Brower's personal gift, and the two scholarships to be known as the "A. Blaine Brower Traveling Scholarships." Also, the Committee had received a request for an appropriation of \$500.00 additionally for the Research Fellowship program for 1951. The Finance Committee recommended approval of these two items, and the Regents by formal resolution agreed.

Dr. Brower then presented detailed operating statements of the College for 1950, analyzed and discussed them and pointed out there will be an estimated surplus in the General Fund for 1950 of about \$54,000.00. Likewise submitted to the Board of Regents were the detailed budgets for the various departments for 1951. The Finance Committee adjusted these to include certain additions, which in their opinion were desirable, and the Board of Regents formally approved. The budget shows an estimated income of \$286,600.00 and an estimated expenditure of \$255,400.00.

At this point Dr. Brower, on behalf of the Finance Committee, introduced the subject of how the cost of the new and revised 1951 Directory should be financed. That is, whether the Directory should be published entirely at College expense and given to all active members free of charge, or whether it be published on the same basis as the 1949 Directory, with a charge of \$4.00 made to all members who wished to subscribe and an increased charge of \$5.00 or \$6.00, according to publication costs, be made to non-members and others desiring to obtain the Directory. After extended discussion, a resolution was adopted directing that the Executive Secretary follow the custom of 1949, by which pre-publication orders shall be received from members at \$4.00, with the exception of Life Members, to whom the Directory shall be furnished without charge.

Dr. Brower reminded the Board of Regents that the budget for 1951 provides for reimbursing Governors for one-half their round trip railroad fare to the Annual Session, an experiment begun in 1950 and costing for that year a little over \$4,300.00.

A resolution was then adopted approving the report of the Committee on Finance as a whole.

President Middleton then asked for a report from the newly appointed Committee on Military Affairs through Dr. Richard A. Kern, Chairman.

Dr. Kern stated that the Committee's deliberations thus far were concerned primarily in establishing the military status of our Research Fellows. In the case of those Research Fellows who had already volunteered or had been already called to active duty, the Committee recommended that the College inform the Surgeons General of their respective services, urging assignment to best advantage. In the case of Research Fellows in the midst of their programs, the Committee recommended that the College immediately explore with the Surgeons General of the Army, Navy and Air Force the matter of these men being commissioned as Reserve Officers, their period of active duty to be deferred temporarily, according to the need and the emergency.

Individual cases were reviewed and specific action recommended.

With regard to the function of the Committee on Military Affairs, it was recommended that the Board of Regents notify the Department of Defense, the Selective Service Board and the Surgeons General of the Armed Forces that this Committee has been appointed and is ready to serve them in an advisory capacity in problems of qualification and placement of prospective medical officers for the Armed Forces.

With regard to a policy of the College on residency training programs, in relation to military service by physicians, the following suggestions were offered:

- (1) The College recognizes the basic duty of physicians to render military service.
- (2) Therefore, the College is not in sympathy with any plan of permanent deferment of those in Residency Training.
- (3) However, there is desirable an orderly program of activation with the least possible disruption of programs of Graduate Training of teachers and investigators.
- (4) The College recommends to schools and hospitals the policy that physicians whose residency training is interrupted by military service be assured of the opportunity to resume and complete such training upon termination of the military service.
- (5) The College advises deferment of military service for the period of their Fellowships or Residencies in the case of all physicians (Fellows or Residents) engaged in research in the Basic Science Departments of Medical Schools. It is pointed out that this is numerically a small group, but the more important because most of these engaged in this field are not physicians, but are Ph.D.'s or prospective Ph.D.'s.

With regard to the future selection of A.C.P. Research Fellows, it was suggested:

- (1) Preference might be given to those who have had military service.
- (2) If the earlier-mentioned program of commissioning and deferment of Fellows for the year of the Fellowship finds favor with the Surgeons General of the Armed Forces, then future candidates for Fellowships who are liable to military service should be encouraged to seek Reserve Commissions. This would tend to avoid discrimination against such candidates on the ground that their Fellowships might be interrupted.

By formal resolution, the report of the Committee on Military Affairs was approved.

Announcements were made that the next meetings of the Committee on Credentials will be held at Philadelphia on March 11, 1951, and at St. Louis on April 7, 1951; that the next meeting of the Board of Regents will be held in conjunction with the Board of Governors at St. Louis on April 8, 1951.

Adjournment.

Attest: E. R. LOVELAND,
Secretary

THE MEDICAL STORY OF SAINT LOUIS

Site of the 32nd Annual Session of the American College of Physicians, April 8-13, 1951

THE City of St. Louis, scene of the coming American College of Physicians annual meeting in April, has been somewhat roughly sloganized as "first in shoes, first in booze and last in the American League." With all due regard for the city's large shoe industry, excellent breweries and quite respectable ball clubs, it would seem important to suggest that the remarkable development of the city in the past hundred years into one of the first ranking medical centers in the world should somehow be included in the slogan.

As a delegate to the American College of Physicians meeting, you may be interested in knowing why the city is so regarded. Here is a summary of some of the events which led to its present position in the medical world.

A city acquires its medical reputation through its medical facilities and the men who use them. St. Louis possesses an enviable quantity and



FIG. 1. Downtown St. Louis, looking east to Mississippi River. Large building in foreground is Kiel Auditorium where American College of Physicians annual meeting will take place in April.

quality of both. Briefly, let us examine its facilities, a few of its outstanding medical leaders and their accomplishments and then go back to the small river town, founded before the American Revolution, and sketch its development to the present day.

The St. Louis University School of Medicine is a large, red brick building located on Grand and Caroline Avenues. Since 1933, its facilities for clinical instruction have been ideal due to the erection at that time of the very modern Firmin Desloge Hospital across the street from the school. Other clinical facilities are utilized at St. Mary's Hospital, St. Mary's Infirmary, the St. Louis City Hospital, as well as all but one or two of the Catholic Hospitals in the city. Money has recently been raised to build a



FIG. 2. The modern Firmin Desloge Hospital (left), built in 1933, provides convenient facilities for clinical instructions for students at St. Louis University School of Medicine located across the street.

children's hospital, with superb research opportunities. A cancer hospital is also in prospect. The school has established an international reputation.

The Washington University School of Medicine enjoys, perhaps, even longer established international prestige. Clinical instruction is facilitated by the proximity of the school buildings to the Barnes and St. Louis Children's Hospitals, the McMillan Eye, Ear, Nose and Throat Hospital, the Oscar Johnson Institute (for research and teaching in ophthalmology and otolaryngology), the St. Louis Maternity Hospital and the Mallinckrodt

Institute of Radiology, all closely adjacent to Forest Park. Nearing completion is the Cancer Research Laboratory. To be built in the near future are the David P. Wohl, Jr., Memorial Hospital for cancer patients, and a relocated Bernard Free Skin and Cancer Hospital.

In all, St. Louis boasts more than fifty hospitals and clinics.



FIG. 3. Medical facilities of the Washington University School of Medicine consist in the main of this group of hospitals and clinics adjacent to Forest Park.

NOBEL LAUREATES

It is almost certain that the excellent facilities which have been made available through the progress of the medical schools have in turn made possible the development of outstanding physicians and scientists in many fields.

It is often said that a measure of the eminence of a community in scientific fields is the singling out of its citizens for public honors. Among such honors a Nobel Prize is a preëminent distinction. Six St. Louisans have been awarded Nobel Prizes for research work done in St. Louis, five of these in physiology and medicine, one in the closely allied field of physics. Five of these scientists continue as active contributors to the academic and medical life of our community. The sixth is affiliated with the Rockefeller Institute for Medical Research. The Nobel laureates of St. Louis will

undoubtedly reaffirm in the minds of the members of the American College of Physicians the prominent and vigorous part the city has taken in the field of medicine.

During 1920-1923, Chancellor Arthur Holly Compton of Washington University, working in the university's physics laboratory, made theoretical deductions which indicated that when x-rays reacted with matter, they acted like particles. Thus when x-rays were allowed to fall on carbon and to be scattered in different directions, it was predicted that the scattered x-rays



FIG. 4. Dr. Arthur Holly Compton, chancellor of Washington University, won the 1927 Nobel Prize for contribution in physics.

would lose energy during the impact and the wave length would be increased. Experimental methods were set up for measuring this effect (now known as the Compton Effect), and the exact increase in the wave length predicted by the theory was observed.

Up to that time, most scientists believed that a beam of x-rays consisted of a group of waves. Dr. Compton's work established the dual nature of x-rays. When traveling, they act as waves, and when reacting with matter, they behave as particles. This discovery led to a more complete under-

standing of the nature of matter and radiant energy and opened up one of the most fruitful fields in the investigations of physics.

Dr. Edward A. Doisy, professor of biochemistry, St. Louis University School of Medicine, and Dr. Henrik Dam of Copenhagen were honored in 1943 for their studies upon vitamin K. Dr. Dam had found in 1929-1934 that chicks on experimental diets regularly developed hemorrhages unless certain additions of a hitherto unrecognized dietary essential were made to the diet. He named his new essential factor "Koagulations-



FIG. 5. Dr. Edward A. Doisy, professor of biochemistry at St. Louis University School of Medicine, shared the 1943 Nobel Prize with Dr. Henrik Dam of Copenhagen. The prize was awarded for contribution in physiology and medicine.

vitamen" or vitamin K. In 1935, it was demonstrated that vitamin K is necessary in the formation of prothrombin. Dr. Doisy and his group reported in 1939 the isolation of vitamin K from alfalfa and of vitamin K₂ from putrified fish meal, and presented evidence to indicate a quinoid structure of these vitamins.

Previous to his work with vitamin K, Dr. Doisy had done fundamental work upon the female sex hormones. More recently he has been engaged upon biochemical studies of antibiotic compounds.

Drs. Joseph Erlanger, professor emeritus of physiology, Washington University School of Medicine, and Herbert S. Gasser, formerly professor of pharmacology, Washington University School of Medicine and now with the Rockefeller Institute for Medical Research, were awarded the Nobel Prize for their investigation of the conduction of impulses by nerves. The most significant contribution in this field was the adaptation of the cathode ray oscilloscope for measurement of the action potential along the nerve. By means of this highly sensitive research instrument, they were able to demonstrate that nerve action is carried by individual fibers at different speeds, ranging from above 100 meters per second down to a fraction of a



FIG. 5. Dr. Herbert S. Gasser (left), formerly professor of pharmacology at Washington University School of Medicine and now with the Rockefeller Institute for Medical Research in New York. Dr. Joseph Erlanger (right) is professor emeritus of physiology at Washington University School of Medicine. The prize was awarded for contribution in medicine.

meter per second. The factor determining the speed at which impulses are carried is the size of the individual nerve fiber. Thus it was shown that a nerve such as the sciatic has as many as 4,000 fibers and may be compared to an electric cable having 4,000 conductors all of which conduct electricity at a different speed. It is now believed, but not yet demonstrated, that the total impulse is interpreted by the brain from the pattern transmitted by these separate impulses which have traveled along different fibers and so have arrived at different times.

The doctors Carl F. and Gerty Cori, both professors of biochemistry at Washington University School of Medicine, are the first husband-and-wife team in America to win a Nobel Prize, and the first husband-and-wife team in history to win in medicine. Dr. Gerty Cori is the first woman to win

the award in medicine. The research work for which the Coris were awarded the Nobel Prize was in the field of physiological chemistry. They investigated thoroughly and established the cycle which is required to change glucose into glycogen and glycogen into glucose. This is important, basic scientific information which any physician or scientist must use in studying any disease connected with sugar metabolism. Glucose is the form in which sugar is carried in the blood and, in general, is the form in which it is transported from one part of the body to another. Glycogen, or body starch, is the form in which sugar is stored in the body. Thus, if one wants to investigate any phenomenon involving transporting of sugar and body storage of sugar, the complete chemistry of the cycle is required. One of the most important aspects of the Coris' work was the discovery of the derivative of



FIG. 7. Dr. Carl F. Cori and his wife, Dr. Gerty T. Cori, professors of biochemistry at Washington University School of Medicine, were awarded the Nobel Prize for contribution in medicine.

glucose, glucose-1-phosphate, which is now commonly referred to as the Cori ester and which is actually utilized by the body to form glycogen. Subsequently they isolated and crystallized the enzyme phosphorylase from muscle. It is this enzyme which makes possible the conversion to glycogen.

Thus we find St. Louis today a city with more than its share of medical genius and blessed with a plethora of medical facilities. What conditions, what combination of events brought this about?

EARLY PHYSICIANS

As the "gateway to the West" and later the nation's hub of travel and communication, St. Louis was destined to thrive. As a meeting place,

stopping-off place and major market for all the midwest, it provided an unequaled opportunity for medical practice. From all points of the compass—by river boat, highway and railroad—travelers, traders and the ever-increasing inhabitants of the fertile Missouri and Mississippi Valley came to the bustling city.

The first physician to permanently establish himself in the new village of St. Louis was Dr. Andre Conde who in 1766 was given a grant of two lots from Governor St. Ange on which he built a residence where he remained until his death in 1776. A doctor Valleau arrived in 1767, but died in 1768, leaving the first will to be executed in the new town.

Other early physicians were Dr. Antoine Reynal who appeared in 1776, Dr. Bernard Givkinsin, 1779, Dr. Claude Mercier in 1784 and Dr. Phillip Joachim Gingembre in 1792. All stayed but a short time.

The first physician of note was Dr. Antoine Saugrain, a French chemist born in 1763. His sister was the wife of the famous Dr. J. I. Guillotin of Paris who invented the guillotine. Dr. Saugrain has left interesting records of a trip he made down the Ohio River with three companions, Piquet, Pierce and Roguet. While floating down the river, they were attacked by Indians, and Pierce escaped by swimming ashore; Roguet, whose arm had been broken in the exchange of gunfire, drowned, and Dr. Saugrain and Piquet were taken prisoner. Piquet was stabbed and scalped in full view of Dr. Saugrain, who managed to escape, however, and join Pierce. The two made their way to Louisville, living on the meat of "stinking beasts" or skunks, the chronicle relates.

After living for a while in Gallipolis, Illinois, and other places, Dr. Saugrain came to St. Louis in 1800 where he practiced until his death in 1820. In the Missouri Gazette for May 26, 1809, is an item, "Dr. Saugrain gives notice of the first vaccine matter brought to St. Louis. Indigent persons vaccinated gratuitously." His earnestness and modesty are illustrated by a remark which is said to have been made to his daughter who was his laboratory assistant, "We are working in the dark, my child. I only know enough to know that I know nothing."

Here, indeed, was the ideal type of physician whose high and objective purpose was the search for truth. One can imagine that, under the honest eye of Dr. Saugrain, the village of St. Louis was not much harmed by medical charlatans.

The local contemporaries of Dr. Saugrain were not numerous. Dr. Bernard G. Farrar arrived in 1807 and became the first president of the St. Louis Medical Society when it was founded in 1836. In 1809, Dr. Robert Simpson came, opened a drug store in 1812, was appointed postmaster, later became sheriff, then city comptroller and finally cashier of the Boatmen's Savings Institution. His varied career ended with his death in 1873 at the age of 87.

DR. WILLIAM BEAUMONT

The arrival of Dr. William Beaumont in 1835 gave St. Louis one of its most noteworthy physicians. Dr. Beaumont's observations on the open stomach of a patient, Alexis St. Martin, had been published in 1833. He was assigned to St. Louis as Army surgeon at the U. S. Arsenal and was permitted to have private practice in addition.

In 1840, Dr. Beaumont was one of three physicians who attended a man who had been beaten on the head with an iron cane. Dr. Beaumont removed the spiculae of bone from the skull by trephining. This was done without anesthetic, it being six years before the advent of ether. The patient died and his assailant was tried for murder. The attorney for the defense contended that the operation by Dr. Beaumont and not the blows might have caused death. Three physicians testified that the symptoms did not warrant trephining, and it was also argued that this was one of Dr. Beaumont's experiments in which he was "boring for symptoms"—the same reason he had kept Alexis St. Martin's stomach open.

Dr. Beaumont was made president of the St. Louis Medical Society in January, 1841, and in the presidential address struck back at his enemies in a fiery address, the text of which cannot be found in the minutes or official records of the society. Jesse S. Myers in his "Life and Letters of Dr. William Beaumont," published in 1912, records this address in part: "Does not gratuitous swearing or rank perjury before the courts of law, designed to screen a murderer from condign punishment and blacken the characters and blast the fair reputation of honest and honorable members of the profession go unpunished, unabated and unwhipped of justice?"

As in the case of all progress, the development of new medical technics by Dr. Beaumont and others in St. Louis came in for their share of opposition due to ignorance, fear and jealousy. It is forever to his credit that he fought for what he believed despite bitter criticism. He was honored by the society in 1854 shortly after his death. His name continues to appear in St. Louis as Beaumont Street, Beaumont High School and the Beaumont Medical Building. Each year the Medical Society holds a short commemorative service at his grave in Bellefontaine Cemetery.

DR. CHARLES A. POPE

Dr. Charles Alexander Pope received his medical degree from the University of Pennsylvania in 1839. After studying in Paris, he settled in St. Louis in 1841 where he became professor of anatomy and physiology in the medical department of St. Louis University in 1843. There he continued to teach until his resignation in 1864. He was renowned as a teacher and for 25 years was the leading surgeon of the Middle West.

In 1864, he decided to go abroad for his health. In his farewell address, he said in part, "To Dr. Beaumont I owe much. I honored him while living, and I shall never cease to revere his memory—a man to whom

humanity is debtor, and whose name is immortal. Allusion has been made to my connection with medical teaching in the West. To it I am largely indebted for whatever success has attended my professional efforts. To teach is the best way to learn. It gives edge and accuracy to knowledge." Dr. Pope died by his own hand in Paris in 1871.

DR. JOSEPH N. McDOWELL

Dr. Joseph Nash McDowell was born in Lexington, Kentucky, April 1, 1805. After graduating from the Medical College of Ohio in 1825, he continued his studies in Philadelphia, specializing in anatomy. In 1840, he came to St. Louis where he organized a medical college. His students idolized him because of his teaching ability and entertaining manner. In 1861, he abandoned his college and joined the Confederate Army. The Union forces took over his college and converted it into a military prison. When Dr. McDowell returned five years later, there was little left but the bare walls and for a while he practiced in Cairo, Illinois. He died in September, 1868, of lobar pneumonia and was buried in Bellefontaine Cemetery.

HISTORY OF MEDICAL EDUCATION IN ST. LOUIS

Dr. McDowell's school, organized in 1840, precipitated St. Louis into a period of activity in medical education which has persisted to the present time. More than 30 medical colleges were chartered between 1840 and 1900. At one period there were four times as many medical schools operating in St. Louis as there are now in the entire state of Missouri. Most of them were short-lived, as they deserved to be because of their low standards and today only two schools survive. Both of these became medical departments of universities.

ST. LOUIS UNIVERSITY MEDICAL SCHOOL

Although the present St. Louis University Medical School came into being less than 50 years ago, the university first sponsored a medical school in 1842. On its first faculty was the young physician previously mentioned, Dr. Charles A. Pope, who contributed so much teaching skill and organizational ability that he soon became dean, and the school became known colloquially as "Pope's College." In 1855, due to the political "Know Nothing" agitation, St. Louis University and the medical college amicably parted ways, the latter continuing as the St. Louis Medical College and eventually becoming a part of Washington University.

St. Louis University again entered the field of medical education in 1903, when it acquired the property and good will of two medical schools which had combined resources two years before. The Marion Sims (1890) and Beaumont (1886) Medical Colleges, both with short but creditable histories, believed that amalgamation and adoption by the university would prove of mutual benefit. The dean of the new department and the president of the



FIG. 8. Dr. Melvin A. Casberg, dean of St. Louis University School of Medicine.

university recognized the great importance of building a reorganized school of medicine around a number of capable and outstanding teachers and research workers. This was accomplished without delay.

Under the leadership of such men as Dr. Young H. Bond, Rev. John C. Burke, S. J., Dr. Hanau W. Loeb, Dr. Charles Hugh Neilson and Rev. Alphonse M. Schwitalla, S. J., the department has grown and become prominent.

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

The medical department of Washington University was formed in 1899 by the union of the first two medical schools established west of the Mississippi River—the St. Louis Medical College and the Missouri Medical College. The latter was originally the proprietary college of Dr. Joseph Nash McDowell who, as previously mentioned, initiated its program in 1840. Early in its existence it was for a brief period the medical department of Kemper College and for another 10-year period was the medical department of the University of Missouri. In 1891, the St. Louis Medical College (Pope's College) affiliated with Washington University and eight years later

combined with "McDowell's College" as the official medical department of this university. In 1910, taking cognizance of criticisms made by Abraham Flexner in his survey of medical schools, Washington University undertook a wholesale reorganization of its medical education program. Outstanding young physicians such as George Dock, Joseph Erlanger, Eugene Opie, Robert J. Terry and Philip Shaffer were brought in as full-time professors of clinical and pre-clinical departments. Great credit for the inspiration and financial assistance for this work must go to Robert S. Brookings, then president of the board of directors, later founder of the Brookings Institute.

In any summary of this kind many important figures and events must of necessity be passed over. I have attempted only to touch the high spots of St. Louis' development into its present world renowned position in medicine. I have attempted to show how a combination of circumstances—geographic location, inspired medical pioneers and high standards set by the organizers of our medical colleges and their successors—have contributed to bring this about. It will be immediately obvious to those who are at all familiar with the personal achievements of the city's physicians, surgeons and researchers that much in this regard has necessarily been omitted in this brief article.

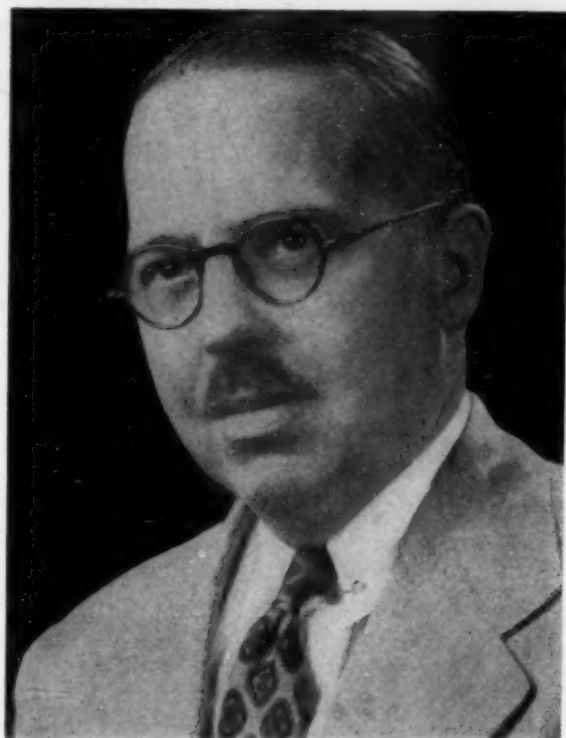


FIG. 9. Dr. Robert Moore, dean of Washington University School of Medicine.

And, now, a final word regarding St. Louis' qualifications as a host to visitors. Though its fine symphony orchestra and Municipal Opera will not be performing at the time of the meeting, there are many other worthwhile places of entertainment and interest. The world famous Missouri Botanical (Shaw's) Garden with its 12,000 species of plants gathered from all parts of the earth, the City Art Museum with its excellent collection of classic and modern paintings, the St. Louis Zoo, which is among the best in the country, are a few of the city's unusual possessions. You will find also that St. Louis is justly famous for its cuisine and fine hotels.

These, and other aspects of our city, will help you understand why, ever since the great World's Fair of 1904, people have been saying with pleasure, "Meet Me in St. Louis!"

